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BORDEN S. VEEDER
St. Louis
Editor

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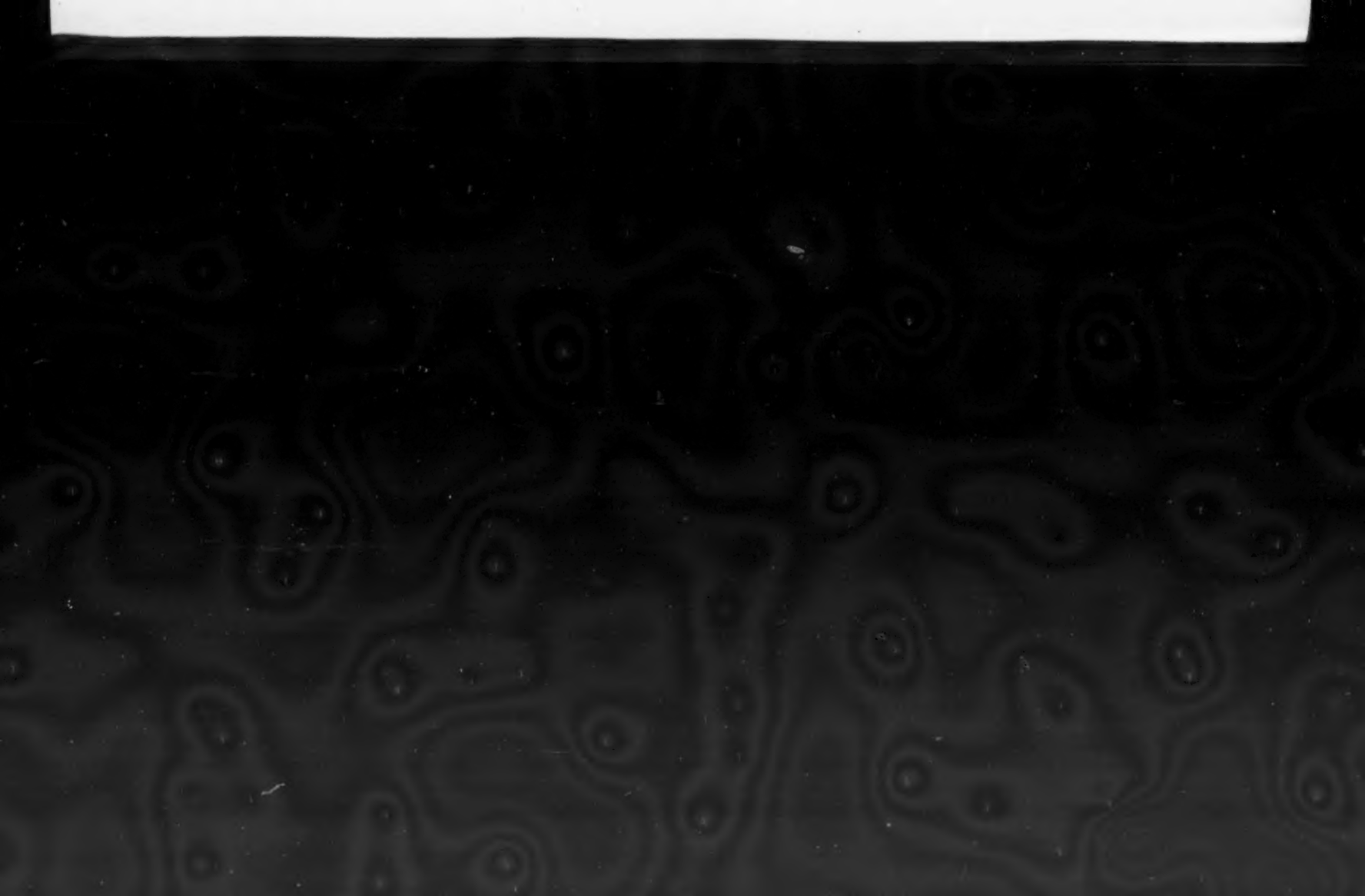

The Journal of Pediatrics

VOL. 31 NOVEMBER, 1947 No. 5

Original Communications

BLOOD VOLUME IN CONGENITAL HEART DISEASE

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CHICAGO, ILL.

I. THE ABNORMAL CIRCULATION IN CONGENITAL HEART DISEASE

THE concept of congenital heart disease as a form of abnormal arteriovenous or venoarterial fistula is not new. Halstead[1] suggested that the persistent ductus arteriosus should be considered as an arteriovenous fistula, the pulmonary artery and the right side of the heart representing the venous side of the fistula, the enlargement of the left side of the heart being analogous to the dilation of the artery proximal to a fistula, and the dilation of the right side of the heart and pulmonary artery being analogous to the dilation of the veins. Holman,[2] in addition, included the patent interventricular septum and the foramen ovale as examples of arteriovenous communications which should have the same physiologic effects on the circulation as a peripheral fistula. He divided these communications into two varieties, intracardiac and extracardiac. In the intracardiac form, the shunt occurs within the heart, and in the extracardiac form outside of the heart. A simple form of intracardiac arteriovenous fistula is a defect in the interauricular or interventricular septa. The ductus arteriosus which is patent represents an extracardiac arteriovenous fistulous communication. More complicated forms of abnormal communications are commonly seen.

This abnormal fistulous flow initiates an accessory circulation and imposes upon the normal blood flow an added volume of blood. This additional blood recirculates through a vascular path determined by the site of the shunt. The concept of an accessory or "third" circulation imposed and parasitic upon the systemic or pulmonary circulation identifies the vascular and cardiac paths involved in the recirculation of shunted blood and indicates the cardiac chambers whose burden is increased. This "third" circulation must be filled by (1) reduction of blood flow distal to the fistula, (2) an increase in blood volume, or (3) both.

From the Pediatric Department, The University of Chicago.
This work has been supported by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

With intracardiac shunts, the flow must be different than in extracardiac communications, since the continuity of flow is interrupted by diastole. In the case of an interventricular septal defect the abnormal flow between chambers takes place during systole and even then the right ventricle rapidly diminishes in size during this period. Pressure relationships during diastole are not favorable for interventricular flow. These circumstances are in contrast to the continuous though uneven flow through the extracardiac fistula, where the pressure gradient in diastole as well as in systole is sufficient to maintain the abnormal arteriovenous flow.

This circulation can be shown diagrammatically. Fig. 1 represents the accessory circulation initiated by a patent ductus arteriosus, an abnormal extracardiac arteriovenous communication. Since this shunt is continuous and the recirculation involves the pulmonary vascular bed, the magnitude of this circulation is considerable. Figs. 2 and 3 show uncomplicated intracardiac arteriovenous shunts through defective auricular and ventricular septa. In Fig. 4 the venoarterial shunt of the tetralogy of Fallot originates within the heart, but the complete accessory circulation includes peripheral vascular paths.

It is not suggested that the blood filling this "third" circulation retains its identity and continues to recirculate in the same way. It is believed, however, that these paths are distinct and separate from the standpoint of dynamics and volume.

II. THE BLOOD VOLUME

The effect of a peripheral arteriovenous fistula or aneurysm on the circulation has been the subject of considerable clinical and laboratory investigation. McGuire and associates[3] have listed these circulatory changes in two categories, those generally accepted and those which remain under discussion. The effect of such an abnormal communication on the blood volume has not been clearly demonstrated, and the blood volume in congenital heart disease has not been adequately studied.

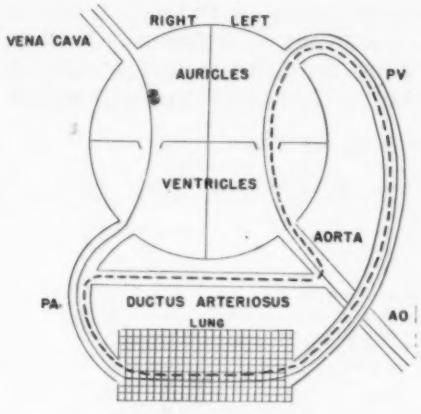
The blood volume, therefore, was determined in normal subjects and in patients having congenital heart disease. The method used for these determinations has been described by Gibson and Evans[4] and by Gibson and Evelyn.[5] The blood volumes of normal children are shown in Fig. 5 in their relation to surface area. Any standard of reference for the comparison of children of varying sizes is open to question, but surface area has been chosen since it has been shown[6] to give truer estimations of the blood volume of normal children. The range of variation of the blood volumes of normal children about the trend lines is used in the present study as a basis for comparison with patients having congenital heart disease.

The patients with congenital heart disease studied represent three general groups: (I) acyanotic congenital heart disease, (II) patent ductus arteriosus, and (III) cyanotic congenital heart disease. Of these categories, Group II is the only one in which a specific anatomic diagnosis has been made. Group I is composed of patients who have congenital heart disease without cyanosis, and represents intracardiac arteriovenous shunts. Group III contains those cases of

congenital heart disease where there is constant cyanosis and is not representative of a single specific anatomic defect.

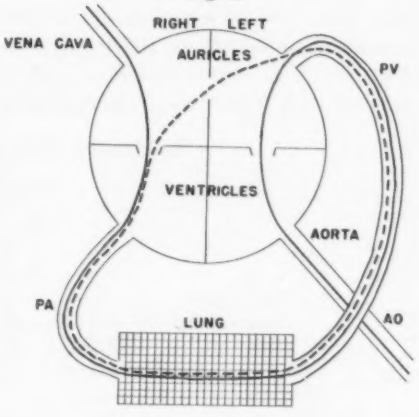
Patients in whom abnormal shunts were absent, as those with aortic stenosis or coaretation of the aorta, have been omitted.

Fig. 1.

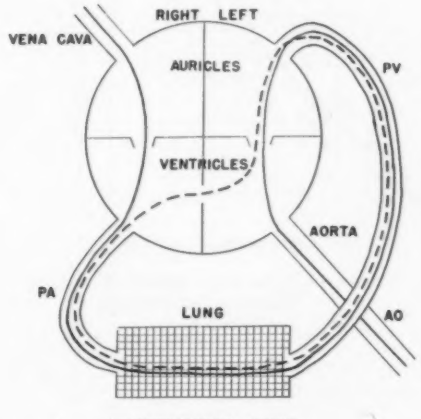


ARTERIO-VENOUS SHUNT
PATENT DUCTUS ARTERIOSUS

Fig. 2.

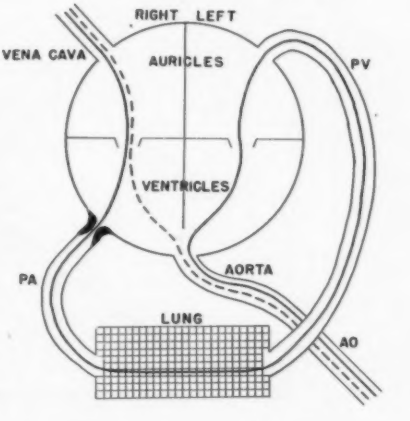


ARTERIO-VENOUS SHUNT
INTERAURICULAR SEPTAL DEFECT



ARTERIO-VENOUS SHUNT
INTERVENTRICULAR SEPTAL DEFECT

Fig. 3.



VENOUS-ARTERIAL SHUNT - TETRALOGY OF FALLOT

Fig. 4.

Figs. 1, 2, 3, and 4.—Showing an abnormal accessory circulation in the presence of patent ductus arteriosus, interauricular and interventricular septal defects, and the tetralogy of Fallot. The normal circulation is represented diagrammatically by a solid line. The abnormal accessory circulation due to the congenital defects is shown as a broken line. In the tetralogy of Fallot, the abnormal accessory circulation includes peripheral paths.

Figs. 6, 7, and 8 show the blood volumes of the three varieties of congenital heart disease in relation to the blood volumes of normal children. The age, height, weight, plasma volume, hematocrit, and total blood volume of the patients are shown in Tables I and II.

DISCUSSION

Holman, in several papers,[2, 7-9] has argued for the increase of blood volume as a compensatory mechanism necessary in the presence of any considerable abnormal arteriovenous communication. He demonstrated this increase following the production of experimental arteriovenous fistulas, and showed a fall in blood volume following the surgical closure of fistulas in patients. Further, the blood volume was shown to rise following the experimental production in dogs of an intracardiac arteriovenous shunt, an interventricular septal defect.[2]

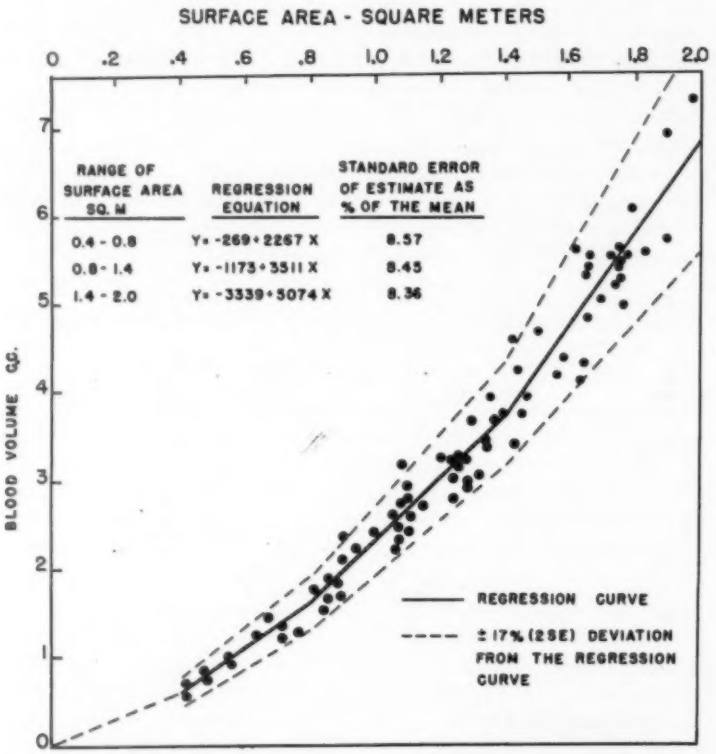

SURFACE AREA - SQUARE METERS
0 .2 .4 .6 .8 1.0 1.2 1.4 1.6 1.8 2.0
BLOOD VOLUME CC.
0 1 2 3 4 5 6 7
RANGE OF SURFACE AREA SQ. M
REGRESSION EQUATION
STANDARD ERROR OF ESTIMATE AS % OF THE MEAN
0.4 - 0.8 Y= -269+2267 X 8.57
0.8 - 1.4 Y= -1173+3511 X 8.45
1.4 - 2.0 Y= -3339+5074 X 8.36
REGRESSION CURVE
± 17% (2SE) DEVIATION FROM THE REGRESSION CURVE

Fig. 5.—Blood volume of normal children.

Several cases of congenital heart disease were analyzed from the standpoint of chamber enlargement, and evidence adduced indirectly to substantiate the concept of an increase in blood volume as a corollary to an abnormal arteriovenous communication, although measurements were not reported.

Reid and McGuire[10] believed they could not confirm these observations either in the production of arteriovenous fistulas in dogs or by surgical repair of fistulas in patients. McGuire and associates,[3] however, reported increase in total blood volume in dogs following the production of fistulas surgically.

Kennedy and Burwell[11] found an increase in the blood volume in a patient with an arteriovenous fistula. Warren and associates[12] studied the blood volume before and after operation in over forty patients and found a significant decrease in one-third, generally in patients with clinical evidence of a large fistula.

The relation of patency of the ductus arteriosus to the blood volume was studied by Eppinger and associates.[13] They reported an increased blood volume following the experimental production of a ductus in dogs and a decrease in volume in patients as a result of surgical ligation of the patent ductus.

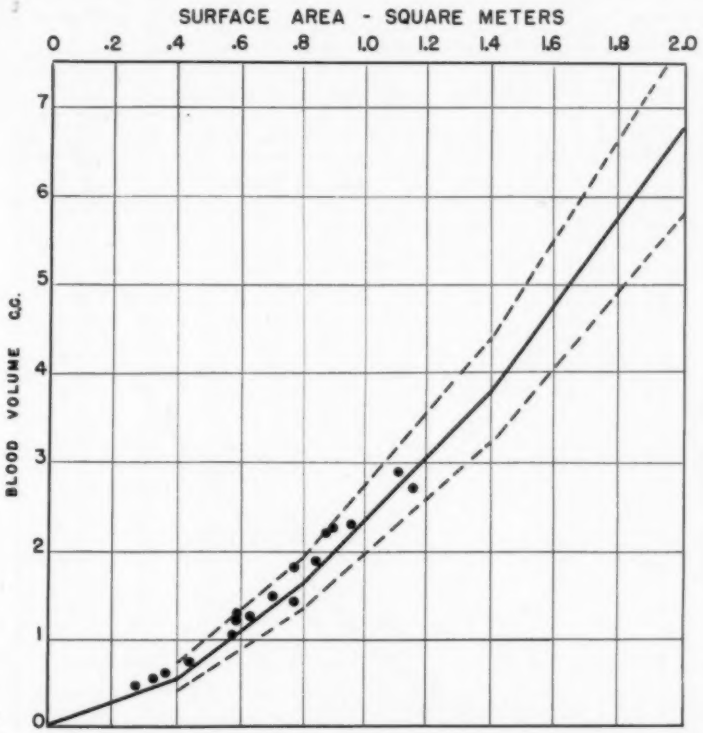


Fig. 6.—Blood volume in acyanotic congenital heart disease.

Hallock[14] pointed out that there are few available studies of blood volume in cyanotic congenital heart disease. He determined the plasma volume, the circulating red blood cell mass, and the total blood volume in four patients who were markedly cyanotic. The total circulating red blood cells and total blood volume were elevated, but the absolute plasma volumes were lower than expected. This suggested an attempt to prevent the total blood volume from increasing a maximum amount following the increase of red blood cells as a result of anoxic stimulus. This fall in plasma volume was not found to be present in polycythemia vera.

We have found an elevation of the blood volume in the three categories of congenital heart disease into which the patients were divided. In the type of extracardiac shunt representing an arteriovenous fistula, the patent ductus arteriosus, the blood volume was elevated when compared with the values obtained in normal children (Fig. 6). In thirteen patients who had unequivocal signs of uncomplicated patent ductus arteriosus, only one had a blood volume below the mean normal value, and four had volumes greater than two standard errors of estimate. In seven of eight instances where the blood volume was determined before and after ligation, there was a decrease in the volume following surgery. This is shown in Table III. The patent ductus arteriosus is associated with an increase in volume of the circulating blood.

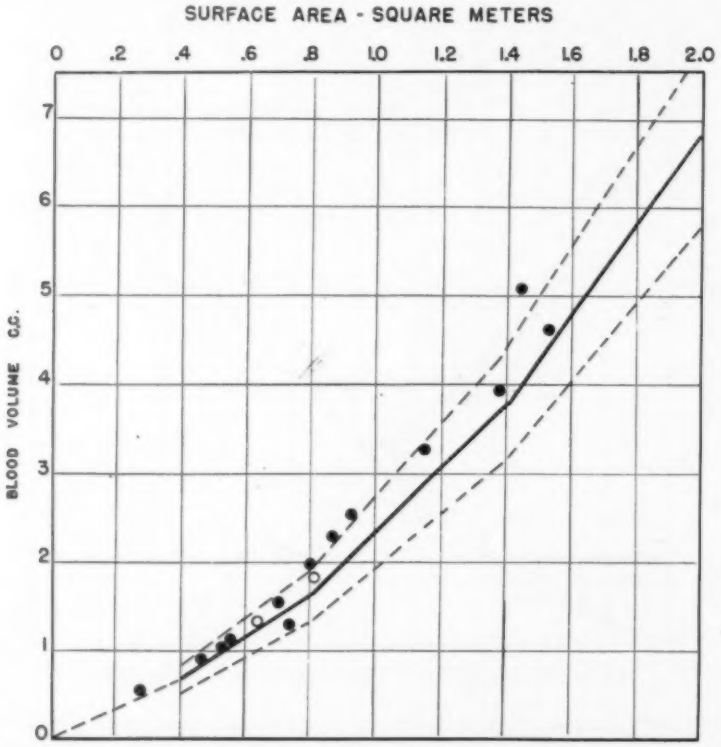


Fig. 7.—Blood volume in the patent ductus arteriosus. Open circles represent two cases of peripheral, congenital arteriovenous fistula.

The group consisting of intracardiac shunts without cyanosis also showed an elevation of blood volume, although this increase was of less magnitude than in patients with a patent ductus, as is shown by comparison of Figs. 6 and 7. Since it has been suggested that in these the shunt is intermittent and absent during diastole, the lower volume is expected if it is assumed that the volume is

TABLE I. DATA OF PATIENTS REPRESENTED IN FIGS. 6 AND 7.

PATIENT	AGE (YR.)	SEX	HEIGHT (CM.)	WEIGHT (KG.)	SURFACE ($M.^2$)	HEMATOCRIT (%)	PLASMA VOLUME (C.C.)	CELL VOLUME (C.C.)	TOTAL BLOOD VOLUME (C.C.)
Patent Ductus Arteriosus									
G.F.	0.83	F	68	4.6	0.29	36.7	329	189	515
J.McC.	2.00	M	81	11.0	0.48	37.3	573	341	914
D.S.	3.00	M	91	13.0	0.56	38.7	656	413	1,069
C.P.	3.33	F	96	12.2	0.57	41.2	637	446	1,083
M.B.	3.83	M	105	16.8	0.70	35.4	975	532	1,507
A.C.	5.58	F	108	18.6	0.74	41.7	773	552	1,325
J.F.	6.42	F	116	20.5	0.81	39.0	1,235	793	2,028
K.K.	8.08	F	122	22.1	0.87	38.4	1,388	867	2,255
B.S.	10.50	F	129	23.7	0.93	41.7	1,462	1,020	2,482
H.B.	10.58	M	142	33.0	1.15	39.0	2,006	1,328	3,334
I.T.	13.50	M	162	51.6	1.54	42.8	2,625	1,964	4,590
V.A.	13.68	F	158	42.7	1.39	40.5	2,350	1,600	3,950
E.J.	31.00	M	164	44.1	1.45	46.0	2,814	2,396	5,210
Congenital Arteriovenous Aneurysm									
K.B.	3.67	F	102	15.7	0.66	38.8	796	504	1,300
M.P.	7.58	M	119	20.2	0.83	40.3	1,114	753	1,867
Acyanotic Congenital Heart Disease									
S.E.	0.33	F	61	4.9	0.28	34.3	294	153	447
M.N.	0.42	M	—	5.5	--	36.5	372	214	586
V.S.	0.68	F	70	5.8	0.33	35.7	360	200	560
S.H.	1.00	F	70	7.5	0.37	32.9	409	201	610
D.G.	1.25	F	87	7.3	0.43	35.3	454	247	701
M.K.	3.00	F	97	13.8	0.60	36.6	771	485	1,256
J.H.	3.50	M	92	15.0	0.60	38.2	726	448	1,174
G.L.	3.50	F	96	12.8	0.58	40.4	626	425	1,051
M.M.	4.08	F	102	14 4	0.64	43.0	712	537	1,249
M.C.	6.00	F	116	19.4	0.79	41.2	823	576	1,399
S.C.	6.00	F	115	18.1	0.77	41.4	1,001	707	1,708
W.McG.	6.33	M	117	23.1	0.86	42.2	1,085	794	1,879
S.G.	6.83	F	114	15.2	0.71	39.1	872	559	1,431
W.H.	8.67	M	128	25.9	0.96	39.5	1,347	878	2,225
W.G.	9.33	M	122	21.5	0.86	43.4	1,229	941	2,170
P.S.	9.42	M	127	21.5	0.88	34.0	1,420	732	2,152
M.D.	12.33	F	139	31.2	1.11	38.7	1,759	1,111	2,870
N.J.	13.25	F	145	32.5	1.16	38.3	1,665	1,035	2,700

directly related to the degree of shunt. The increased volume in the presence of the intracardiac shunt unfortunately could not be compared with change in volume resulting from surgical repair of the shunt. Statistical analysis, however, has shown a significantly greater blood volume in this group than in normal children.

The great increase in the blood volume in cyanotic heart disease is striking. (Fig. 8) The increased total blood volume is due entirely to the great increase of circulating red blood cell volume, and, as Hallock[14] found, there is usually a decrease in the expected plasma volume. It would appear that under the conditions of body economy in the presence of cyanotic congenital heart disease, an increase in viscosity is preferred to a still greater increase in total blood volume. Dill[15] has suggested that increased viscosity due to polycythemia is, perhaps, not an important factor in circulatory adjustments. Table II shows details of the plasma and red blood cell volumes in these patients.

With great increase in total blood volume due to increased volume of red blood cells, the increase of volume due to intracardiac shunt is obscured, and there is no apparent way to separate the factors involved. It seems likely that the increased volume due to shunt would be small in comparison with the increase due to polycythemia. It also seems likely that the effect of shunt would be present, since there is no reason to suppose that the influence of a venoarterial shunt differs in this regard from an arteriovenous shunt.

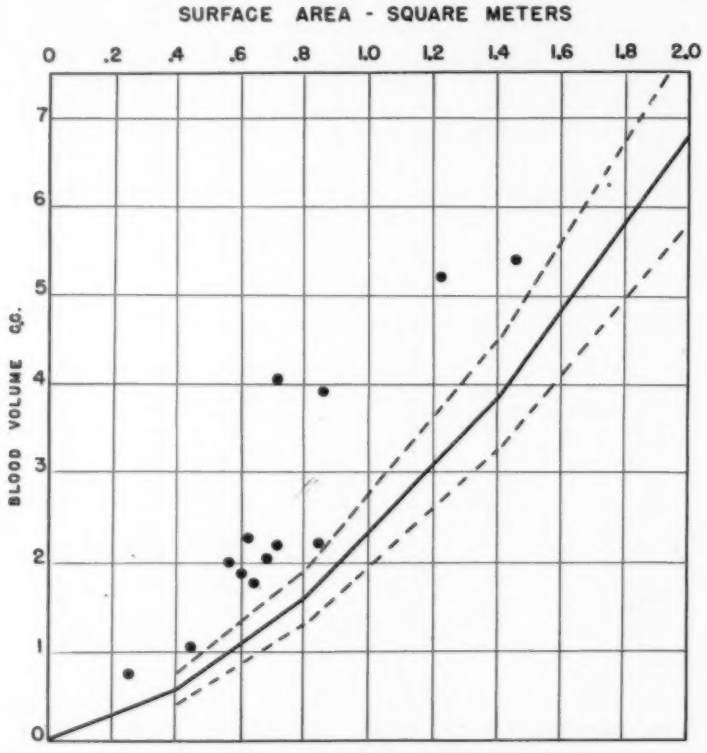


Fig. 8.—Blood volume in cyanotic congenital heart disease.

The relations of the blood volumes in the three categories to those of normal children and to each other are shown in Fig. 9 in terms of the per cent deviations of the individual blood volumes from the volumes estimated from surface area. While the chart shows variations within each group, it emphasizes differences in distribution between the groups which have been shown by Fisher's "t" test to be statistically significant.

The nature of the stimulus for blood volume increase in arteriovenous communications is not clear. It is presumed that volume is required because of an increase in the vascular bed and collateral channels. It is believed that the concept of a "third" circulation is sound, and that this accessory circulation

requires a certain volume of blood to fill it. Increase in volume to the equivalent of the abnormal shunt as suggested by Holman[2] is not easily proved since the volume required to sustain the shunt may be readily found by diminished flow to other parts of the body. Blood flow distal to the patent ductus arteriosus may be decreased significantly. The increase in peripheral blood flow fol-

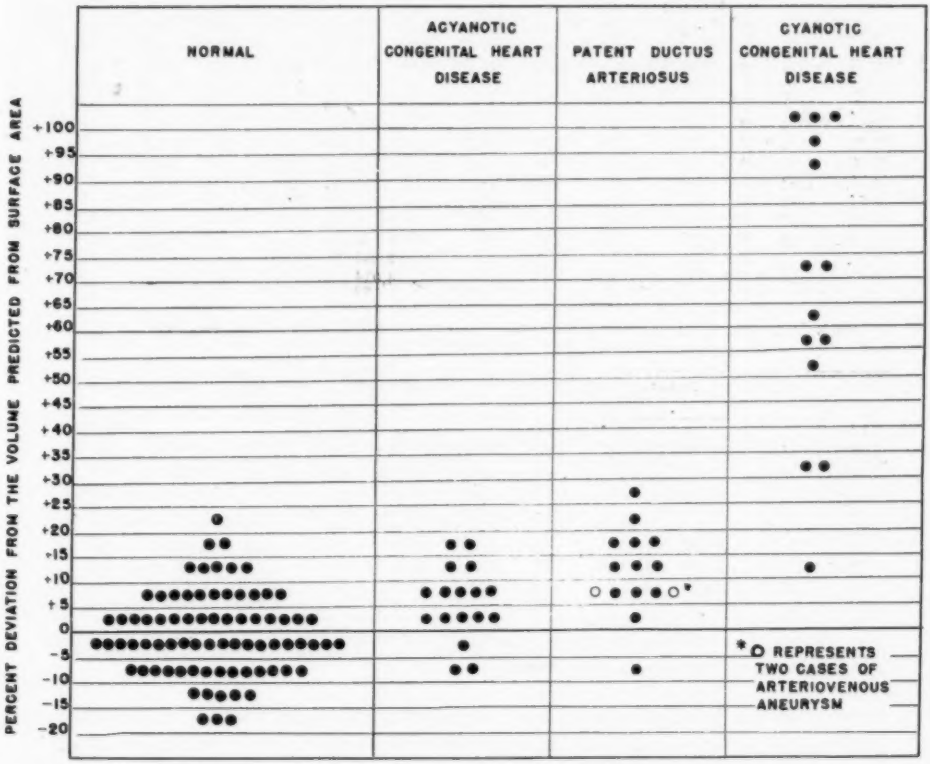


Fig. 9.—Relation of blood volume of the three groups of congenital heart disease to each other and to blood volume of normal children, shown graphically.

lowing ligation of the patent ductus arteriosus may be the stimulus for the accelerated growth in children which is frequently observed. Quantitative measurements of the peripheral flow before and after ligation are not available, however.

SUMMARY

The abnormal circulation in congenital heart disease is in many respects similar to the abnormal circulation in a peripheral arteriovenous fistula, although the vascular paths of the shunted blood are shorter. This communication is continuous in an extracardiac fistula, as the patent ductus arteriosus, and intermittent in intracardiac shunts, the septal defects. The abnormal

TABLE II. CYANOTIC CONGENITAL HEART DISEASE: DATA OF PATIENTS IN FIG. 8.

PATIENT	AGE (YR.)	SEX	HEIGHT (CM.)	WEIGHT (KG.)	SURFACE (M.²)	HEMATOCRIT (%)	PLASMA VOLUME (C.C.)	CELL VOLUME (C.C.)	TOTAL BLOOD VOLUME (C.C.)	DEVIATION FROM THE NORMAL VOLUME AS PREDICTED FROM SURFACE AREA		
										PLASMA (%)	CELLS (%)	WHOLE BLOOD (%)
R.B.	0.33	M	64	3.8	0.26	65.2	254	476	730	+26	+117	+74
S.K.	1.75	F	84	9.5	0.46	75.4	252	773	1,025	−47	+157	+32
N.H.	3.50	M	95	14.5	0.61	61.5	704	1,123	1,827	+19	+156	+64
J.G.	4.50	F	99	15.0	0.64	66.4	597	1,180	1,777	+17	+134	+50
C.F.	4.08	M	93	13.5	0.58	78.6	430	1,579	2,009	−16	+284	+92
R.B.	6.83	M	98	14.8	0.62	70.2	661	1,547	2,218	−4	+347	+95
R.B.	6.83	M	112	17.2	0.73	67.7	698	1,463	2,161	−17	+167	+56
V.S.	6.92	F	106	15.7	0.68	65.8	693	1,331	2,024	−10	+165	+59
J.M.	7.92	M	109	16.1	0.71	86.1	558	3,456	4,014	−31	+553	+199
D.M.	8.08	M	123	21.8	0.87	52.9	1,015	1,138	2,153	−10	+52	+14
R.D.	8.67	M	—	19.3	--	85.5	586	3,454	4,040	−35	+393	+152
S.D.	10.50	M	125	21.0	0.87	76.3	952	2,888	3,840	−16	+286	+104
R.A.	12.17	M	148	35.5	1.22	71.9	1,524	3,896	5,420	−17	+207	+74
B.N.	16.17	M	159	47.9	1.47	64.5	1,921	3,494	5,415	−21	+167	+31

TABLE III. CHANGES IN BLOOD VOLUME FOLLOWING LIGATION OF THE PATENT DUCTUS ARTERIOSUS*

PATIENT	AGE	PLASMA VOLUME C.C.			HEMATOCRIT %			TOTAL BLOOD VOLUME C.C.		
		BEFORE	AFTER	DIFFERENCE	BEFORE	AFTER	DIFFERENCE	BEFORE	AFTER	DIFFERENCE
DS	3.08	656	617	−39	38.7	36.6	−2.4	1,069	973	−96
MB	3.83	975	953	−22	35.4	38.6	+3.2	1,507	1,552	+45
JF	6.42	1,235	1,128	−107	39.0	40.9	+1.9	2,028	1,908	−120
KK	8.03	1,390	1,135	−255	38.4	40.4	+2.0	2,256	1,904	−352
BS	10.50	1,448	1,420	−28	41.1	38.7	−2.4	2,459	2,316	−143
HB	10.58	2,006	1,916	−90	39.0	39.1	+0.1	3,294	3,146	−148
VA	13.58	2,350	2,219	−131	40.5	42.9	+2.4	3,933	3,836	−97
EJ	31	2,808	2,749	−59	46.0	47.1	−4.3	5,200	4,715	−485

*With one exception (VA), blood volumes were determined two to three weeks following the ligation of the ductus. The blood volume of VA was determined five months after ligation and was corrected for increase in growth.

communication initiates an accessory circulation which, in relation to dynamics and volume, is independent of the systemic or pulmonary circulation upon which it is parasitic. The accessory or "third" circulation in several simple congenital cardiac defects is illustrated. The relation of the abnormal circulation to the circulating blood volume is considered.

The volume of the circulation was determined by the blue dye method in three categories of congenital heart disease, (1) intracardiac acyanotic shunts, (2) patent ductus arteriosus, and (3) cyanotic congenital heart disease. The values obtained were compared with the blood volume of normal children.

The blood volume in patients with a patent ductus arteriosus was found to be increased, and the volume diminished following surgical ligation of the open ductus. The blood volume in acyanotic intracardiac arteriovenous shunts was elevated by a smaller amount. The volume in the cyanotic type of congenital heart disease was greatly increased, due to an increase of red blood cells. The plasma was usually below the expected amount.

It was concluded that the abnormal circulation in the three categories of congenital heart disease requires an elevation of circulating blood volume. It could not be determined whether this increase is a direct measure of the abnormal shunt.

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COMPARATIVE ABSORPTION, EXCRETION, AND STORAGE OF OILY AND AQUEOUS PREPARATIONS OF VITAMIN A

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In 1946, Clifford[1] reported that aqueous preparations of vitamin A (Vi-Penta and ViSyneral) brought about higher vitamin A blood levels in premature infants than did the oily product (Oleum Percomorphum). These aqueous preparations contain vitamin A alcohol dispersed in a watery solution of propylene glycol or glycerin, whereas the oily product consists of vitamin A esters of the higher fatty acid group dissolved in fish liver oil. Other differences between these two types of vitamin A preparations are the presence in the aqueous product of vitamin B components, ascorbic acid, and solubilizers.

As indicated in Table I, observations which we made on the Premature Ward at Bellevue Hospital are in complete agreement with Clifford's findings. Thus, in eight premature infants receiving the oily preparation containing 35,000 units of vitamin A, the average rise of vitamin A in the blood at five hours was 62 units, whereas with the aqueous preparation, the average rise was 274 units per 100 c.c. plasma.

The present study was undertaken to ascertain whether the same phenomenon obtained for full-term infants and children. Accordingly, six full-term infants, ranging in age from one to 3 months, were given 35,000 units of vitamin A of the oily preparation (Oleum Percomorphum) and several days later they received the same amount of vitamin A incorporated in an aqueous preparation (Vi-Penta). Blood samples were taken for vitamin A determination prior to, and three, six, nine, and twenty-four hours following, the administration of vitamin A. It should be added that the original concentration of vitamin A in the oily preparation was 60,000 units per cubic centimeter, whereas the potency of the aqueous preparation was 10,000 units per cubic centimeter. In order that these preparations have comparable vitamin A concentrations, the oily preparation was diluted with cottonseed oil, so that the resulting potency was 10,000 units per cubic centimeter.*

The method employed for the vitamin A determination was the same as we used in our previous investigations[2] and is based on the Price-Carr reaction. The intensity of the blue color following the addition of antimony trichloride was measured in an Evelyn photoelectric colorimeter, using a 620 μ filter.

The results of this experiment are revealed in Chart 1. In all six infants, the vitamin A blood levels were considerably higher following the administration

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*It should be added that this precaution was unnecessary, as it was subsequently determined that the vitamin A blood levels were of the same order for the diluted and undiluted oily preparation.

TABLE I. VITAMIN A BLOOD LEVELS IN PREMATURE INFANTS FIVE HOURS FOLLOWING THE ADMINISTRATION OF OILY AND AQUEOUS PREPARATIONS OF VITAMIN A (35,000 UNITS).

CASE	WT. (LB.)	PREPARATION	VITAMIN A CONCENTRATION IN BLOOD (UNITS PER 100 C.C. PLASMA)			
			FASTING	5 HOURS	RISE	
					OILY	AQUEOUS
Fa	5¼	Oily	118	208	90	
Ev	4¾	Aqueous	77	220		143
El	4⅛	Oily	86	120	34	
Za	5¼	Aqueous	84	435		351
Jo	4¾	Oily	117	129	12	
Al	4½	Aqueous	164	270		106
Av (1)*	5¼	Oily	56	86	30	
Av (1)	4½	Aqueous	134	603		469
Av (2)*	4½	Oily	78	204	126	
Av (2)	5¼	Aqueous	52	370		318
Ha	5	Oily	52	73	21	
Ba	4⅛	Aqueous	142	693		551
Al†	5½	Oily	87	236	149	
Al†	5¾	Aqueous	71	193		122
Hi†	4¾	Oily	52	89	37	
Hi†	5¾	Aqueous	74	212		138
				Av.	62	274

*Twins.
†Same infant.

of the aqueous preparation. It may be noted that in two infants, Fr and Ka, there was almost no rise following the administration of the oily preparation in contrast to the significant elevation in vitamin A blood levels following the aqueous product. The average maximal vitamin A blood rise with the aqueous preparation was 1,000 units, whereas the average maximum rise with the oily preparation was only 200 units.

In Chart 2 are illustrated the vitamin A blood levels in older children following the administration of the two vitamin A preparations. The dose of vitamin A administered was 5,000 units per pound body weight. Again, the vitamin A concentrations in the blood were much higher following the aqueous preparation; the average rise of the vitamin A blood concentration was 4,000 units for those children receiving the aqueous product and 600 units for those receiving the oily preparation.

It was of interest to determine whether the striking difference in vitamin A blood levels also would occur in adults following the ingestion of the oily and aqueous preparations. Six adults were given 500,000 units of vitamin A in oily and aqueous vehicles and the vitamin A blood levels were determined three, six, and, in some instances, nine and twenty-four hours following the administration of vitamin A. The results of these tests are revealed in Chart 3, where, it will be noted, in all six adults the blood levels again were considerably higher following the ingestion of the aqueous preparation. The average maximal rise in vitamin A concentration was 4,500 units for those adults receiving the aqueous preparation and 1,750 units for those receiving the oily product.

The question arises as to the significance of these widely divergent blood levels. The possible explanations are: (1) a pronounced difference in the intestinal absorption of vitamin A, the aqueous preparation being better absorbed

than the oily preparation; (2) a difference in the rate of absorption, the aqueous product being absorbed much more rapidly and, therefore, resulting in a higher blood level. Although the oily preparation might be more slowly absorbed, at the end of twenty-four or forty-eight hours the total absorption might be the same for both preparations. If this were true, the difference in blood levels would be more of academic than practical interest; (3) The high vitamin A blood level might be due to a lag in the withdrawal of vitamin A from the blood into the body stores as a result of the aqueous diluent, the intestinal absorption being the same for both preparations.

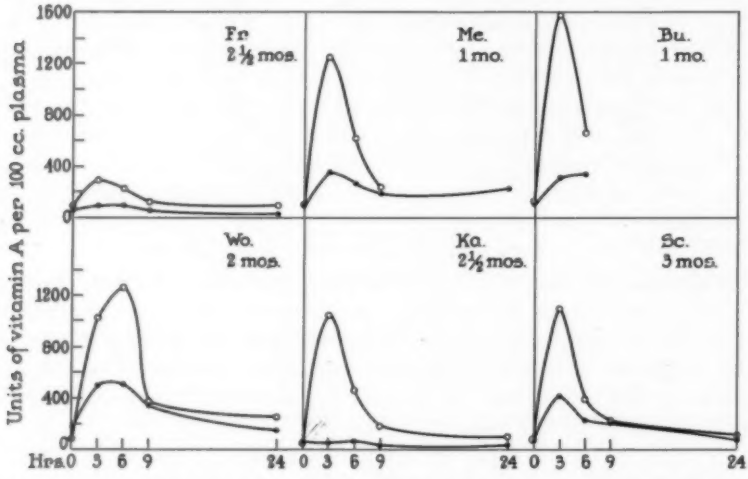

Chart 1.—Vitamin A blood levels in infants following the administration of 35,000 units of vitamin A in oily and aqueous vehicles.

• Oily preparation.
○ Aqueous preparation.

In order to evaluate the aforementioned possible explanations for the differences in blood levels following the two types of vitamin A preparations, a study of the fecal excretion of vitamin A was carried out. Seven infants were given one dose of either 12,500 or 35,000 units of the oily preparation. Stools were collected for twenty-four hours prior to and for six days following the administration of vitamin A. When the excretion of vitamin A in the stools dropped to a basal level, a comparable amount of vitamin A of the aqueous preparation was administered and the stools were collected as above. It should be added that the stools were kept on ice and each twenty-four hour collection was assayed immediately for vitamin A.

The method employed for the vitamin A determination of stools was similar to that which we employed previously in assaying the vitamin A content of liver.[3] Inasmuch as we found that the vitamin A remains stable in stools for periods of forty-eight to seventy-two hours, we were certain that no deterioration of vitamin A took place in the stools during the twenty-four-hour period in which they were collected.

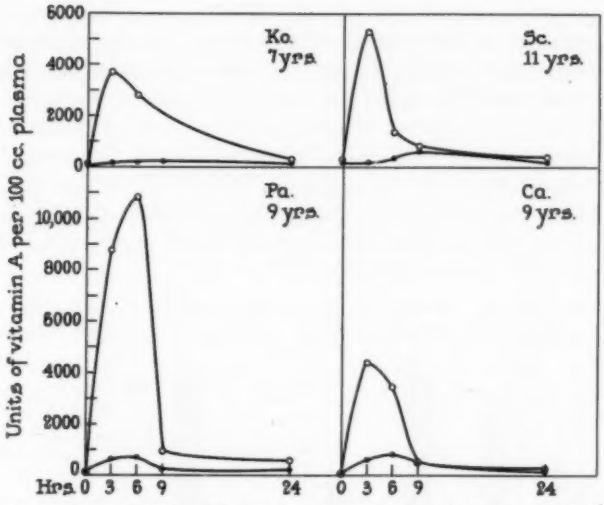

Chart 2.—Vitamin A blood levels in children following the administration of vitamin A in oily and aqueous vehicles (5,000 units per pound body weight).

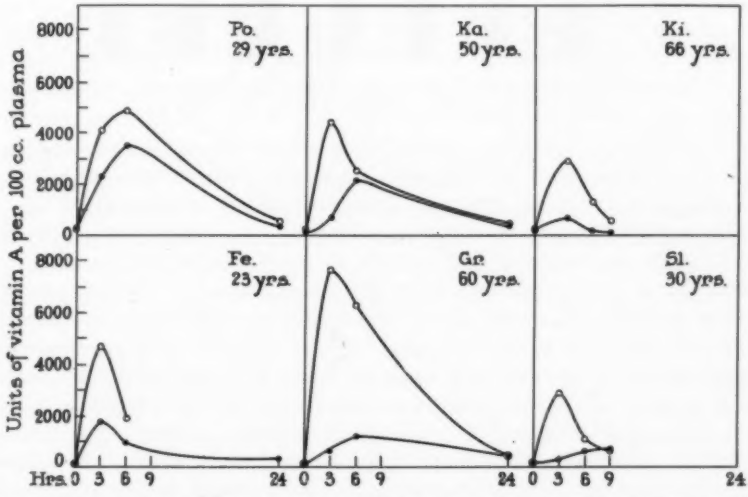

Chart 3.—Vitamin A blood levels in adults following the administration of 500,000 units of vitamin A in oily and aqueous vehicles.

The results of fecal excretion are illustrated in Chart 4. It will be noted that in every instance there was greater excretion of vitamin A with the administration of the oily product. The amount of vitamin A excreted in the stools in the seven infants varied from 11 to 60 per cent of the intake following the oily preparation and from 2 to 17 per cent following the aqueous preparation. The average fecal excretion was 38 per cent of the amount of vitamin A ingested when the oily product was given, whereas, only 7 per cent of the vitamin A intake was excreted in the stools when the aqueous preparation was given. The excretion of vitamin A was of the same order of magnitude whether the dosage was 35,000 or 12,500 units. The latter dosage is the amount of vitamin A which is generally given to infants when the oily preparation is prescribed (10 drops of the commercial oily product contain 12,500 units).

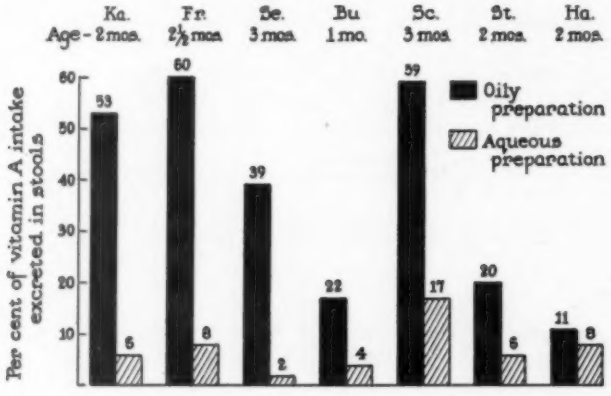

Chart 4.—The fecal excretion of vitamin A in infants following the administration of 12,500 or 35,000 units of vitamin A in oily and aqueous vehicles.

These results, therefore, indicate that the oily preparation was poorly absorbed and, conversely, the aqueous preparation was well absorbed. Thus, it may be concluded that the wide divergence in vitamin A blood levels was due to a marked difference in the absorption of these two vitamin A preparations.

The final criterion, however, in the evaluation of the oily and aqueous preparations would seem to rest on the comparative storage of vitamin A in the body following their administration. Information of this kind obviously could not be obtained from human investigation. If it could be demonstrated that animals respond to the oily and aqueous preparations in the same manner as humans, a study of the comparative storage of vitamin A in animals following the administration of these products would have direct application to man. We, therefore, decided to undertake an investigation of the absorption, excretion, and storage of aqueous and oily preparations of vitamin A in rats and in guinea pigs.

One hundred and ten rats weighing 125 to 150 Gm. were given a single dose of 13,000 units of vitamin A and seventy-four guinea pigs weighing 350 to 400 Gm. were given 39,000 units of vitamin A incorporated in the oily and aqueous

preparations. The rats received the vitamin by stomach tube because it was discovered that they rejected the aqueous preparation when it was fed by tuberculin syringe. Bloods were obtained from the heart for vitamin A analyses three, six, nine, and twenty-four hours after the administration of the vitamin. Animals were sacrificed at the time of bleeding in order to determine the amount of vitamin A stored in the livers at varying times following the administration of the two preparations.

Fecal excretion following the aqueous and oily preparations of vitamin A was studied in twelve rats and in twelve guinea pigs. Stools were collected for one day prior to and for three days following the administration of the vitamin.* As in infants, the stools were assayed for vitamin A at the end of each twenty-four-hour period.

The results of the investigation carried out in rats are illustrated in Chart 5. It will be noted that the vitamin A blood levels were much higher in animals receiving the aqueous preparation. Thus, the average vitamin A concentration in the blood following the administration of the aqueous product was 2,460 units per 100 c.c. plasma at three hours, 2,010 units at six hours, and 310 units at twenty-four hours, whereas, following the oily preparation the average vitamin A blood level was 900 units at three hours, 1,015 units at six hours, and 120 units at twenty-four hours.

The average fecal excretion of vitamin A was 2,930 units when the oily preparation was given, as compared with 645 units when the aqueous product was administered. Rats receiving vitamin A in an oily vehicle excreted 23 per cent of the amount ingested, whereas those receiving vitamin A in an aqueous menstruum excreted 5 per cent of the intake. Thus, rats responded to the oily and aqueous preparations of vitamin A in the same manner as did humans, from the standpoint of vitamin A blood concentrations and fecal excretion.

The results of the vitamin A analyses of the livers of rats receiving both preparations are also shown in Chart 5. Prior to the administration of vitamin A, the average concentration in the liver was 55 units per gram of liver. Following the administration of the aqueous preparation, the liver stores increased to 450 units per gram of liver in three hours, to 680 units in six hours and to 1,150 units in twenty-four hours. On the other hand, the oily preparation of vitamin A increased the liver stores to 130 units per gram in three hours, to 300 units in six hours, and to 670 units in twenty-four hours. The average amount of vitamin A stored in the whole liver twenty-four hours after the administration of the aqueous preparation was 7,500 units, or 58 per cent of the amount of vitamin A ingested, whereas 4,040 units, or 30 per cent of the vitamin A intake, was stored in the liver twenty-four hours after the administration of the oily preparation. These data, therefore, indicate that the storage in the liver was considerably higher following the administration of the aqueous preparation.

The result of the study in guinea pigs is represented in Chart 6. Again, it will be noted that there is a sharp distinction in the vitamin A blood levels

*The excretion of vitamin A in the stools was negligible four days after the administration of the vitamin.

following the oily and aqueous preparations, the vitamin A concentration in the blood being much higher in the guinea pigs receiving the aqueous product. Thus, the average concentration of vitamin A in the blood of animals receiving the aqueous preparation was 1,750 units per 100 c.c. plasma at three hours, 660 units at six hours, 410 units at nine hours and 100 units at twenty-four hours, whereas, following the oily preparation the vitamin A blood levels were 390 units at three hours, 360 units at six hours, 330 units at nine hours, and 190 units at twenty-four hours.

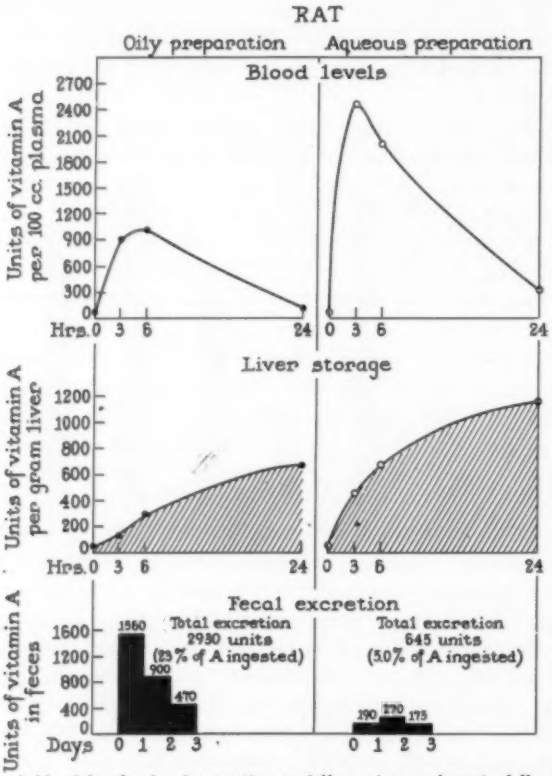

Chart 5.—Vitamin A blood levels, fecal excretion and liver storage in rats following the administration of a single dose of 13,000 units of vitamin A in oily and aqueous vehicles.

The data on fecal excretion reveal that, as in infants and rats, the excretion of vitamin A was much higher in those animals receiving the oily preparation. Thus, 10,800 units of vitamin A, or 28 per cent of the amount ingested, was excreted in three days following the administration of the oily product, whereas 2,550 units, or 6½ per cent of the vitamin A intake, was excreted in the stools when the aqueous preparation was administered.

The liver storage of vitamin A in guinea pigs receiving the oily and aqueous preparations of vitamin A is also shown in Chart 6. The vitamin A concentra-

tion in the liver following the aqueous preparation rose from 37 units per gram to 240 units in three hours, to 264 units in six hours, to 281 units in nine hours and to 390 units in twenty-four hours; whereas following the oily preparation the vitamin A concentration in the liver increased to 78 units per gram in three hours, to 117 units in six hours, to 170 units in nine hours, and to 295 units in twenty-four hours. The average amount of vitamin A stored in the whole liver was 6,090 units when the aqueous preparation was administered, whereas 3,870

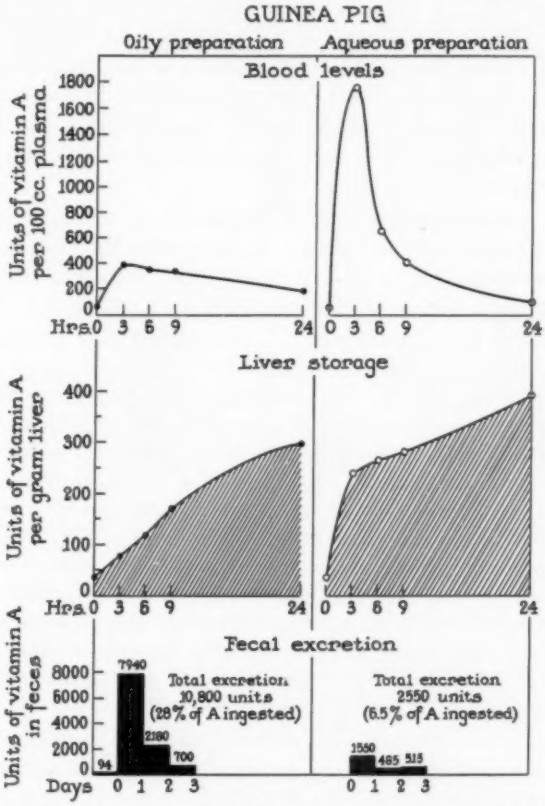

Chart 6.—Vitamin A blood levels, fecal excretion, and liver storage in guinea pigs following the administration of a single dose of 39,000 units of vitamin A in oily and aqueous vehicles.

units were stored in the liver when the oily preparation was given. In other words, 16 per cent of the vitamin A intake was stored in the liver following the administration of the aqueous preparation, as compared with 10 per cent following the oily product. It is apparent from these data that guinea pigs do not store vitamin A as well as rats, under the conditions of this experiment. However, the liver storage in guinea pigs receiving the aqueous preparation was significantly greater than in those receiving the oily preparation.

The dosage of vitamin A administered to the rats and guinea pigs, it may be recalled, was very large, 13,000 units to rats weighing 125 to 150 Gm. and 39,000 units to guinea pigs weighing 350 to 400 Gm. The question may be raised whether smaller doses of vitamin A dispersed in the oily and aqueous vehicles, and given over a longer period of time, would also disclose similar differences in blood levels, in fecal excretion and in liver storage. To obtain this information, twelve guinea pigs, weighing 350 to 400 Gm. were divided into two groups; one group received daily for two weeks 1,000 units of vitamin A of the oily preparation and the other received 1,000 units of the aqueous product. A dosage of 1,000 units is comparable, on the basis of body weight, to the amount of vitamin A which is generally given to young infants (10 drops of the commercial oily preparation are usually prescribed to young infants and contain 12,500 units; infants weighing 5 kg. would, therefore, receive 1,000 units per 400 Gm. of body weight).

Three hours after the last dose of vitamin A was administered, bloods were obtained for vitamin A determination. Stools were collected daily, being assayed in twenty-four-hour collections. At the end of two weeks, the animals were sacrificed, the livers being removed for vitamin A analysis.

The results of this experiment are illustrated in Chart 7. It will be observed that, as in animals which had received very large amounts of vitamin A, the blood levels were higher, the fecal excretion lower, and the storage greater following the administration of the aqueous preparation. Thus, the vitamin A concentration of blood was 360 units per 100 c.c. of plasma in the aqueous group, as compared with 220 units in the oily group. The daily fecal excretion of vitamin A in the guinea pigs receiving the aqueous preparation was 65 units, or 6½ per cent of the intake, in contrast to 260 units, or 26 per cent of the intake in animals receiving the oily product. The liver stores were 166 units per gram for the aqueous group and 91 units for the oily group. The amount of vitamin A which was stored in the whole liver during the two-week period was 2,730 units, or 21 per cent of the vitamin A intake in guinea pigs fed the aqueous preparation, in contrast to 1,170 units, or 9 per cent of the intake, in animals given the oily product.

The results of the animal experiments, therefore, indicate that, as in man, the aqueous preparation of vitamin A was better absorbed than the oily preparation. In view of the fact that the storage of vitamin A in the liver was larger in rats and in guinea pigs with administration of the aqueous preparation, one is justified in concluding that, in humans, too, superior storage of vitamin A would result following the ingestion of the aqueous product.

It would be of great interest and of clinical importance to determine whether aqueous preparations of vitamin A are well absorbed in individuals having disorders which bring about poor absorption of fat, as, for example, cystic fibrosis of the pancreas and obstructive jaundice. It may be recalled that in these conditions the absorption curve following oily preparations of vitamin is flat, or almost flat.

We therefore carried out studies on the absorption of the aqueous preparation of vitamin A in an 8-year-old child having cystic fibrosis of the pancreas and in an adult having complete obstruction of the common bile duct. The dose of vitamin A was 250,000 units for the boy (5,000 units per pound body weight) and 500,000 units for the adult. The vitamin A concentration in the blood was determined three, six and nine hours following the administration of the vitamin.

The data obtained from these blood analyses are illustrated in Chart 8. It will be noted that in both instances excellent rises in the concentration of vitamin A in the blood occurred following the administration of the aqueous preparation, whereas, as was expected, the absorption curve was flat following the oily product.*

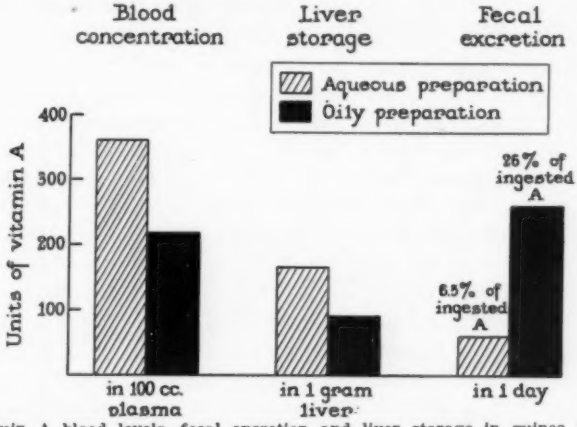

Chart 7.—Vitamin A blood levels, fecal excretion and liver storage in guinea pigs receiving 1,000 units of vitamin A in oily and aqueous vehicles daily for two weeks.

These results indicate the usefulness of the aqueous preparation of vitamin A in conditions affecting the absorption of fat. In view of the fact that vitamin A deficiency is frequently a complication of cystic fibrosis of the pancreas and is an important factor in the morbidity and mortality of this disease, the administration of an aqueous preparation of vitamin A may play a significant role in improving its prognosis.

DISCUSSION

It may be recalled that the vitamin A constituent of the aqueous and oily preparation was not the same, vitamin A alcohol being present in the former and vitamin A ester in the latter product. The question may be raised whether vitamin A alcohol is absorbed better than the ester, and, as a corollary, whether

*In this connection it should be mentioned that Clausen and his co-workers[4] recently reported that the vitamin A alcohol is better absorbed than the ester in cystic fibrosis of the pancreas. Our aqueous preparation, as previously stated, contained vitamin A alcohol. As will be discussed later in this report, we found no difference in the absorption of the alcohol and ester forms of vitamin A in normal subjects. The average maximal rise in the vitamin A concentration in the blood following the administration of vitamin A alcohol in an oily vehicle was 700 units per 100 c.c. plasma. If we assume that the child having cystic fibrosis of the pancreas absorbed vitamin A alcohol in oil as well as normal children, the rise in vitamin A blood level would have been only 700 units as compared with 5,100 units which was obtained following the administration of the aqueous preparation.

the superiority of the aqueous preparation may be attributed to the presence of vitamin A alcohol, rather than to the vehicle. In this connection it should be added that, according to Clausen and his co-workers,[4] vitamin esters require hydrolysis by lipolytic enzymes in the intestine before being absorbed. The end product of the splitting up of the esters are vitamin A alcohol and fatty acids. Vitamin A is absorbed as the alcohol but is re-esterified in the intestinal wall. It is conceivable that the esters may fail to undergo complete hydrolysis and therefore may not be as well absorbed as one of its end products, vitamin A alcohol.

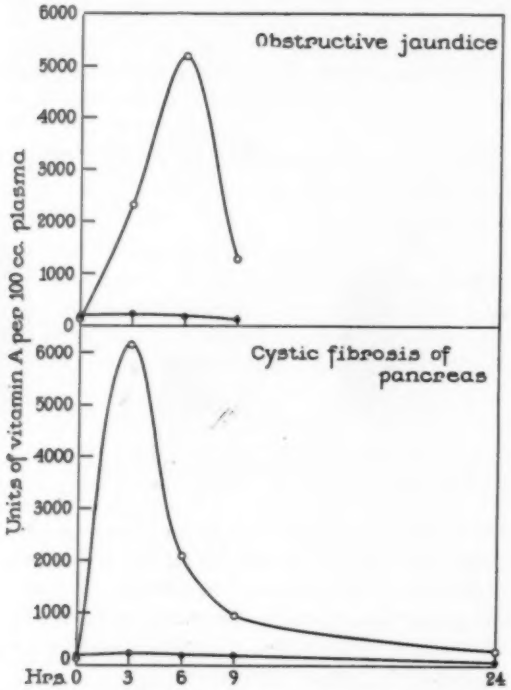

Chart 8.—Vitamin A blood levels following the administration of the oily and aqueous preparations of vitamin A in cases of cystic fibrosis of the pancreas and obstructive jaundice.

In order to evaluate the role of vitamin A alcohol as a possible factor in the superior absorption of the aqueous product of vitamin A, absorption studies of this substance dissolved in oil were carried out on rats, guinea pigs, and children. Similarly, vitamin A esters were dispersed in an aqueous solution to ascertain whether this type of vehicle would enhance the absorption of the esters. The results of this experiment, as well as other studies bearing on the possible factors contributing to the superior absorption of the aqueous preparation, will be reported in detail in another communication. Suffice it to say that the data indicated that there was no difference in the absorption of the alcohol and ester

forms of vitamin A. Furthermore, the presence of vitamin B components and ascorbic acid had no effect in increasing the absorption of vitamin A.

The aqueous preparation which we used in this investigation contained 47 per cent propylene glycol, 53 per cent water, and a solubilizer, mannitan monolaurate. Experiments in rats and in guinea pigs indicated that the solubilizer was an important factor in the aqueous preparation, as a 47 per cent propylene glycol solution of vitamin A without mannitan monolaurate brought about lower blood levels and poorer storage than a 47 per cent propylene glycol solution of vitamin A containing the solubilizer.

The role of the concentration of propylene glycol in the absorption of vitamin A was also investigated. Groups of guinea pigs and rats were given vitamin A dispersed in 100 per cent propylene glycol and in 100 per cent water. Although these preparations effected better absorption of vitamin A than did the oily product, the results were not as good as those obtained with the 47 per cent propylene glycol solution of vitamin A. It should be mentioned, in this connection, that we have recently carried out, in children, absorption studies of vitamin A distilled esters dispersed in an aqueous solution of carbohydrate (dextrimaltose) containing no propylene glycol and no solubilizer. Nonetheless, the absorption curves were just as good as those obtained with the aqueous preparations containing 47 per cent propylene glycol and a solubilizer. It is apparent, therefore, that aqueous vehicles other than the one we used in this investigation may have the same beneficial effect on the absorption of vitamin A.

The results of the experiments reported in this communication must bring about a qualification of our ideas on vitamin A requirements. The reports in the literature on the vitamin A requirements of animals and humans have been based on data obtained with the use of oily preparations. Thus, the minimum requirements of vitamin A for rats,[5] cattle, swine, sheep,[6] and infants[7] have been found to be 25 to 35 units per kilogram of body weight. It is obvious that the requirements will be lower when aqueous preparations of vitamin A are given.

The importance of the vehicle in the absorption of other vitamins, particularly the so-called fat-soluble vitamins, requires investigation. In previous communications, one of us[8] emphasized the role of the menstruum in the effectiveness of vitamin D. Thus, the antirachitic vitamin dissolved in propylene glycol and dispersed in the daily quota of milk was more effective in the prevention and cure of rickets than was the administration of the vitamin in an oily vehicle. It would be of considerable interest to compare the relative value of the oily and aqueous preparations of vitamin K in controlling hypoprothrombinemia.

SUMMARY

The administration of an aqueous preparation of vitamin A brought about much higher blood levels of vitamin A in infants, children, and adults than did an oily preparation.

The fecal excretion of vitamin A was determined in seven infants receiving vitamin A dispersed in an oily and in an aqueous vehicle. The amount of vitamin A excreted in the stools was considerably higher when the oily preparation

was given. Thus, 38 per cent of the vitamin A intake was recovered in the stools when the oily preparation was administered, as compared with an excretion of 7 per cent following the ingestion of the aqueous product. These results, therefore, indicate that the oily preparation was poorly absorbed and, conversely, the aqueous preparation well absorbed, and explain the wide divergence of blood levels following both preparations.

Experiments in guinea pigs and in rats revealed the same findings, namely, higher blood levels and lower fecal excretion of vitamin A following the administration of the aqueous preparation. Furthermore, the vitamin A storage in the liver was considerably higher when the aqueous preparation was given.

In conditions affecting the absorption of fat, as, for example, cystic fibrosis of the pancreas and obstructive jaundice, the administration of vitamin A dispersed in an aqueous vehicle brought about excellent rises in the vitamin A concentration in the blood, in contrast to the flat absorption curve obtained with the use of an oily preparation.

The oily product contained vitamin A esters dispersed in fish liver oil, whereas the aqueous preparation consisted of vitamin A alcohol dispersed in an aqueous solution of propylene glycol containing vitamin B components, ascorbic acid, and a solubilizer, mannitan monolaurate. Experiments carried out in rats, in guinea pigs, and in children indicated that the superiority of the aqueous preparation was not due to the presence of vitamin A alcohol, vitamin B components, or ascorbic acid, but rather to the dispersion of vitamin A (by means of the solubilizer) in an aqueous—propylene glycol vehicle.

We wish to express our appreciation to Miss Mildred Weinstock and Miss Evelyn Morrison for their technical assistance.

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FEBRILE CONVULSIONS: A CLINICAL STUDY WITH SPECIAL REFERENCE TO HEREDITY AND PROGNOSIS

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THE literature of childhood convulsions deals chiefly with three aspects: their etiology, their mechanism, and their relation to the chronic convulsive disorders of later life.

The first aspect has been studied by Peterman,[1] who demonstrated that convulsions occur most frequently during the first three years of life. During this period they are most commonly associated with acute infections and are, therefore, generally called febrile convulsions. In his recent study, Crump[2] has also found that the peak in the age of distribution of childhood convulsions was from 6 months to three years. In this age group, 35.7 per cent of convulsions were associated with acute febrile illnesses.

The role played by fever in the etiology of convulsions has been studied in animals by Wegman.[3] He arrived at the conclusion that two factors were important: the age of the animal and the rapidity with which the body temperature rose. Under the conditions of his experiments, the majority of young kittens developed convulsions; the adult cats did not. The more rapidly the body temperature was raised, the more frequently did convulsions occur. Yannet and Darrow[4] investigated the chemical changes occurring in the brain, liver, and muscles of these experimental animals. They failed, however, to find an explanation for the mechanism of convulsions.

The third aspect, the relation of childhood convulsions to chronic recurrent convulsions of later life (epilepsy), is most controversial in the literature. Hammond[5] and Walton and Carter[6] claimed that there was no relationship between infantile convulsions and epilepsy. An opposite view was expressed by Townsend,[7] Theimisch, and Birk.[8] Osler[9] stated that 40 per cent of his epileptic patients gave a history of infantile convulsions. Still[10] observed that 28 per cent of infantile attacks merged directly into epilepsy. Patrick and Levy[11] obtained a history of infantile convulsions in 20 per cent of their epileptic patients in contrast to 4 per cent of their nonepileptic patients. Thom's[12] recent study indicated that the occurrence of epilepsy was twelve times more frequent in those who had suffered from convulsions in infancy than in those who had not.

The above workers included in their analyses all types of childhood convulsions, regardless of the etiologic basis. Since it is well recognized that certain types of childhood convulsions, such as those associated with birth injuries, meningitis, encephalitis, spontaneous infantile convulsions, are more apt to be

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followed by convulsions in later life, it is possible that these varied conclusions might be explained by the fact that they are based on different material.

Of all the various types of infantile convulsions, those associated with acute febrile illnesses (the so-called febrile convulsions) are encountered most frequently. Therefore, it seemed worth while to make a special study of the prognosis of children whose *first* convulsion was associated with an acute febrile illness.

The subjects for this study were found in a group of over 800 children cared for at the Epilepsy Clinic of the Johns Hopkins Hospital during a period of fourteen years. The patients were referred to the clinic because they had suffered seizures with such frequency as to cause a suspicion of epilepsy. Among this group there were ninety-four patients in whom the first convulsive seizure was associated with an acute febrile illness. The case histories of these ninety-four patients formed the basis of the present study.

The patients were divided into two groups. First, those in whom the initial and each subsequent convulsion was accompanied by fever; and second, those in whom the initial attack was associated with fever, but later attacks sometimes occurred without fever. The recovery rate of each group is shown in Table I. In this table and in all tables to follow, recovery indicates a period of at least two years of freedom from seizures at the time of conclusion of this study.

TABLE I. RECOVERY RATE OF PATIENTS WHO HAD RECURRENT FEBRILE CONVULSIONS ONLY AS COMPARED WITH THOSE WHO HAD RECURRENT FEBRILE AND AFEBRILE CONVULSIONS

	NO. PATIENTS	NO. RECOVERED
Febrile convulsions only	18	18 (100%)
Febrile and afebrile convulsions	76	28 (37%)
Both types	94	46 (49%)

It is to be noted that while the group of patients who had both febrile and afebrile convulsions shows only a 37 per cent recovery rate, 100 per cent of those with febrile convulsions only recovered. The earliest age of cessation of febrile convulsions in our series is 3½ years; the latest age is 8 years; the average age is 6 years.

The race and sex difference of the ninety-four patients was studied with respect to recovery. Seventy-four of the patients were white; twenty were Negro. The sexes were essentially the same in each race. Of the seventy-four white patients, thirty-four (46 per cent) recovered; of the twenty Negro patients, twelve (66 per cent) recovered.

The rate of recovery with respect to the age at the first convulsion is given in Table II.

TABLE II. AGE OF PATIENTS AT TIME OF ONSET OF CONVULSIONS IN RELATION TO OUTCOME

AGE OF ONSET OF CONVULSIONS	NO. PATIENTS	NO. RECOVERED
0-12 month	32	18 (56%)
13-24 months	35	13 (37%)
25-36 months	18	11 (61%)
37 and over	8	4 (44%)
Total	94	46

The earliest age of onset was 3 months; the latest, 8½ years. The frequency of onset was greatest in the first two years, and sharply decreased thereafter. The prognosis seemed not to be influenced by the age of onset.

The relationship of the clinical character of the seizures to the outcome was studied. The patients were divided into two groups; first, those who suffered with recurring generalized convulsions only, and, second, those who at times showed evidence of a focal lesion as manifested by type of seizure. Of the fifty-six patients in the former group, thirty-six (64 per cent) recovered; of the thirty-eight patients in the latter group only ten (26 per cent) recovered.

The relationship of the frequency of the seizures to the prognosis was analyzed. For this purpose the patients were arbitrarily divided into two classes; those suffering less than twenty-four seizures were placed in the "infrequent" group; those suffering twenty-four or more, in the "frequent" group. As would have been expected, the higher rate of recovery prevailed among the "infrequent" group. Fourteen (78 per cent) of the eighteen patients in the "infrequent" group recovered, whereas only twenty-eight (37 per cent) of the seventy-six patients in the "frequent" group recovered.

Of the ninety-four patients studied, sixty-three were treated regularly with the usual anticonvulsant drugs; thirty-one received irregular or no treatment. Of the sixty-three treated regularly, thirty (48 per cent recovered; of the thirty-one who received irregular or no treatment sixteen (51 per cent) recovered. These observations indicate that in this group of patients the prognosis was not influenced by the treatment.

An effort was made to correlate the final outcome of the convulsions with the existence or nonexistence of convulsions in the history of the patient's families (siblings, parents, grandparents, uncles, aunts, and first cousins). In Table III the hereditary background of these patients is separated into three categories; (1) a group having a family history of chronic convulsive disorders (epilepsy); (2), a group with a family history of childhood convulsions only; (3), a group having a family background entirely free of convulsive disorders.

TABLE III. HEREDITARY FACTORS IN THE PROGNOSIS OF CONVULSIVE DISORDERS PRECIPITATED BY FEVER

	POSITIVE FAMILY HISTORY		
	CHRONIC EPILEPSY	CHILDHOOD CONVULSIONS	NEGATIVE FAMILY
Number of patients	17	27	50
Number recovered	5 (29%)	23 (85%)	20 (40%)

It appears in Table III that there is a relatively less favorable prognosis for a convulsive child whose close relatives have suffered from chronic epilepsy; whereas the outcome is better if only childhood convulsions have appeared in close relatives.

These findings strongly suggest that there may be a significant difference between the hereditary factors which predispose to chronic epilepsy and those which predispose to childhood convulsions. Furthermore, patients with a negative family history showed less tendency to recover than those with a family

history of childhood convulsions. This suggests that, in the absence of either type of hereditary predisposition, the occurrence of febrile convulsions may be more commonly dependent upon an exogenous injury to the brain, and thus, be more likely to persist. This suggestion is supported by the clinical observation that in the group with a negative family background were found eight patients showing definite evidence of organic brain damage, whereas only three such patients were found in the group with an epileptic family history and only one in those patients whose relatives had childhood convulsions only.

CONCLUSIONS

In a study of ninety-four patients, each of whose first convulsion in childhood was associated with an acute febrile illness, the following observations were made:

1. The prognosis for recovery in patients whose convulsions were invariably associated with fever was good.

2. The prognosis was better for those patients having fewer recurrent attacks.

3. Focal convulsions carried more serious prognostic importance than generalized convulsions.

4. The prognosis was better in children whose near relatives gave a history of childhood convulsions.

5. Febrile convulsions did not recur after 8 years of age and rarely after 6 years.

6. Age of onset, sex, race, and form of anticonvulsive therapy did not seem to influence the final outcome.

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THE CLINICAL PICTURE OF MUMPS MENINGOENCEPHALITIS AND REPORT OF A CASE WITHOUT PAROTITIS

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DURING the past thirty years there have been increasingly frequent reports of mumps meningoencephalitis, a disease which, nevertheless, remains to most physicians rather rare and ill-defined. No one knows exactly how common it really is, and the reported statistics vary greatly: Dopter,[25] in 1910, found evidence of meningitis in almost 10 per cent of 1,700 French troops with mumps, while Wesselhoeft,[7] in 1933, reported an incidence in Boston of only 0.24 per cent. Most of the early reports of the disease come from France, where it appears to have been fairly common,[2] but cases are found wherever mumps occurs, and the disease should no longer be considered a rarity. Without attempting to review the literature completely, the authors have been able to find reports of 280 cases of mumps meningoencephalitis[1-24] (Table I), and it is on these that the following clinical picture of the disease is based.

Mumps meningoencephalitis can occur at almost any age but, like mumps parotitis, is most common in children and young adults susceptible to the virus. In contrast, there is no apparent reason why the disease should affect males almost four times as frequently as it does females. It is also interesting to note the fairly high (14 per cent) incidence of orchitis in this group of cases, considering that some early French observers believed the disease occurred primarily with orchitis, in children or adults descended from alcoholics or mental defectives. Usually the meningoencephalitis is associated with a clinically evident parotitis, most commonly following it well within seven to ten days' time, but one case of the group appeared as late as twenty-eight days after the parotitis.[19] A not inconsiderable number occur at the same time as the parotitis, and in 9.4 per cent of these 280 cases the meningeal symptoms even preceded the parotitis by one to six days.

The onset of symptoms is invariably acute. In almost all cases (95 per cent), the patient, when able, complains of a headache, usually frontal. Approximately 80 per cent have nausea and vomiting, which may be the main complaints. If the patient is a child, the parents often (53 per cent) remark that he has been very lethargic, or the somnolence is noted later in the disease. Less frequently, the patient has convulsions (11 per cent) or is disoriented (17 per cent) and unable to give a history. On physical examination, the patient is found to have a fever, usually between 100 and 102° F. There are rarely any important physical abnormalities other than variable degrees of meningeal irritation, nuchal rigidity (85 per cent) or abnormal reflexes (69 per cent), such as positive Kernig or Babinski signs. All of these, like the parotitis, may be absent when the patient is first seen, only to appear later in the disease.

From the Army Air Force Station Hospital, Langley Field, Va.

TABLE

AUTHOR	DATE	NO. CASES	RATIO MALE TO FEMALE	NO. CASES PAROTITIS	TIME INTERVAL CNS/PAROTITIS		NO. CASES ORCHITIS	SYMPTOMS AND FINDINGS (NO. CASES)						
					DAYS BEFORE	DAYS AFTER		HEADACHE	VOMITING	STIFF NECK	DISORIENTATION	CONVULSIONS	LETHARGY	REFLEX CHANGES
Kaunitz[1]	1918	3	1/2	3	--	4-14	0	3	3	3	1	1	2	3
Casparis[2]	1919	2	2/0	2	1	--	0	2	1	1	1	1	1	2
Haden[3]	1919	9	9/0	9	1 (1 case)	2-11	4	8	5	8	2	1	4	7
Taillens[4]	1928	1	1/0	1	--	1	0	1	1	1	0	0	1	1
Milo[5]	1931	1	1/0	1	--	5-6	0	1	1	1	1	0	1	1
Paddock[6]	1932	2	2/0	0	--	--	0	2	2	2	0	0	1	2
Wesselhoeft[7]	1933	2	2/0	2	--	6	0	1	1	2	1	1	1	2
Eley[8]	1935	9	7/2	5	2-6 (2 cases)	4-9	0	6	8	7	3	2	7	7
Lassale and Passa[9]	1935	1	1/0	1	4	--	0	NS	0	0	1	0	1	0
Wegelin[10]	1935	1	1/0	1	--	7	0	1	1	1	1	1	1	1
Levy[11]	1936	6	3/3	6	--	2-7	NS	?	NS	?	?	2	?	most cases
Silwer[12]	1936	20	20/0	20	--	0-11	11	20	8	12	NS	NS	NS	6
Finkelstein[13]	1938	4	NS	4	--	up to 7 days	NS	4	4	oc	NS	4	NS	oc
Birnberg[14]	1939	38	29/9	38	--	1-10	NS	38	38?	38	oc	oc	0	38?
Tabor and Newman[15]	1940	29	24/5	29	NS	NS	2	common	common	26	NS	NS	NS	10?
Donahue[16]	1941	1	0/1	1	--	6	0	NS	NS	NS	1	1	NS	1
Frankland[17]	1941	5	5/0	2	--	1-11	2	5	5	5	NS	NS	NS	2?
Hirsch[18]	1942	2	2/0	2	1-2 (2 cases)	--	0	2	0	1	0	0	0	2
Jersild[19]	1942	17	11/6	7	0-3 (2 cases)	0-28	3	16	16	11	26	3	9	15
Neal and Harrington[20]	1942	77	58/19	76	NS	4-5+	6	freq	freq	freq	5	NS	33	freq
Steiner[21]	1942	1	0/1	1	--	7-8	0	1	1	1	0	0	NS	1
Steinberg[22]	1944	10	10/0	10	4 (1 case)	2-10	NS	10	6	10	NS	0	NS	5
Enders and coworkers[23]	1945	33	25/8	17	5-0 (4 cases)	2-5	2	82%	69%	82%	NS	13%	38%	31%
Arey[24]	1946	6	5/1	6	NS	up to 7 days	NS	6	6	NS	NS	NS	6	NS

†NS = Not Stated; *? = Data not clear; pred = predominant; oc = occasional; freq = frequent.

TABLE I

REFLEX CHANGES	DURATION OF SYMPTOMS (DAYS)	DURATION OF FEVER (DAYS)	SPINAL FLUID: NO. CELLS	SPINAL FLUID: LYMPHOCYTES	SPINAL FLUID: PROTEIN	BLOOD: W.B.C.	BLOOD: POLYMORPHONUCLEARS/LYMPHOCYTES	FATALITIES	NO. CASES WITH SEQUELAE
3	2- 4	NS†	99	pred	NS	NS	NS	0	None
2	5	NS	470-900	pred	NS	6,200-15,000	NS	0	None
7	3	2-10	3-780	29-100%	NS	6,200-8,900	40/32-66/60	0	None
1	NS	NS	75	pred	mod. elevation	9,200	63/21	0	None
1	10	5	NS	NS	NS	NS	NS	0	None
2	10	NS	300-880	97-100%	slight elevation	slight elevation	84/16	0	None
2	5- 6	5- 6	426-1,420	pred	NS	9,000	25/75	0	None
7	5- 6	5- 7	31-2,230	75-100%	NS	NS	NS	0	Hemiplegia (1 case)
0	7- 8	7- 8	NS	?*	?*	9,250	54/40	0	None
1	7	NS	NS	pred	NS	NS	NS	1	Death
most cases	NS	NS	270 average	73%	NS	10,320-12,350	70/30	1	Death
6	1- 6	1- 6	3-920	58-100%	slight elevation	NS	NS	0	None
oc	3- 7	NS	increased	pred	increased	normal	normal	0	Toxic psychosis (1)
38?	3-11	2- 8	6-980	82-100%	NS	NS	NS	0	Unil. nerve deafness (1), headache (1)
10?	up to 7-10	NS	100-2,000	pred	NS	NS	NS	0	Retarded in school (4), irritab. (4)
1	death	death	45	90%	NS	NS	NS	1	Death
2?	3- 5	3	230-1,078	"almost all"	NS	NS	NS	0	Headache and depression (1)
2	4-10	NS	270	40%	200 mg. %	4,409-9,400	85/15-90/10	0	None
15	5-10	5-10	100-3,200	pred	slight elevation	NS	NS	0	None
freq	NS	NS	up to 2,120	pred	normal to slight elevation	NS	NS	0	None
1	NS	NS	600	96%	NS	normal	relative lymphocytosis	0	Recurrent meningeal signs—30-60 days
5	3- 6	3- 6	73-602	pred	slight elevation	NS	NS	0	None
31%	7.5	NS	7-1,350	70-100%	25-74	3,000-13,000	average 62/38	0	None
NS	NS	NS	248-880	pred	slight elevation	NS	NS	0	Unil. nerve deafness (1)

Routine blood examinations in these cases yield variable results, white cell counts ranging from 3,000 to 15,000, and a predominance of either the polymorphonuclear leucocytes or lymphocytes. The spinal fluid findings, however, are quite characteristic: the fluid is almost always clear and under normal or only slightly increased pressure, with as many as 3,000, but more commonly 200 to 400 cells, of which at least 70 per cent are lymphocytes. Cases with less than 50 per cent lymphocytes are dubious, although they have been reported.[12] The spinal fluid is, of course, free of bacteria on smear and culture. Usually the protein content is normal, although the level may be as high as 200 mg. per cent. The spinal fluid chloride and sugar levels are rarely abnormal, and only occasionally is the colloidal gold curve abnormal.

The symptoms and clinical signs of the disease seldom last beyond seven to ten days, which has led some observers to state that cases of longer duration are probably not due to mumps.[23] The fever disappears shortly before or with the signs of meningeal irritation, whereas the abnormal spinal fluid findings may last another six or eight weeks.[12] All degrees of severity occur, little fever, or fever lasting a week, few or many clinical signs, high spinal fluid cell counts with few symptoms, or few cells and an alarmingly ill patient, yet the clinical course of these patients is remarkably uniform in the reported cases. The disease is almost always mild: the 1 per cent mortality and the 5 per cent incidence of sequelae in these 280 cases are, no doubt, misleading figures, since the milder cases go unrecognized or unreported.

Many forms of nervous system damage have been ascribed to mumps,[20, 26-30] the most serious being polyneuritis, transverse myelitis, and unilateral nerve deafness, the latter of which, at least, is permanent. It has been estimated that mumps has caused deafness in 5 per cent of the institutionalized deaf in this country. In this series there were two cases of unilateral nerve deafness, an incidence of 0.7 per cent, and one case of hemiplegia. There is little reason to doubt that the cause of these complications, as well as the meningoencephalitis itself, is the mumps virus or its toxic products. Donahue,[16] who found autopsy reports of ten fatal cases in the literature, five of them doubtful cases, and who reported another fatal case, felt that the mumps virus caused the characteristic nervous system lesion he describes, a spotty perivascular demyelinization with neuroglial reaction, "similar to that seen in other post-infection encephalitides." He did not feel that the lesions per se were severe enough to cause death. This would seem to support the impression gained from the 280 cases, that the sequelae, except for the nerve deafness, which is unilateral, are generally mild and transient. Still, they may be more frequent than believed, and have importance as the cause of an otherwise inexplicable irritability or scholastic retardation in a child who has apparently recovered completely from the acute illness.[15]

It is important to suspect and properly to diagnose mumps meningoencephalitis, mainly to avoid treating the patient for other conditions in which specific therapy is indicated. Treatment of the uncomplicated case due to mumps, unlike the treatment of a bacterial meningitis, except probably tuberculous meningitis, is entirely symptomatic. The clinical history, occurrence of

parotitis, and particularly the spinal fluid lymphocytosis will usually differentiate the two. But with ordinary methods the disease cannot definitely be distinguished from preparalytic poliomyelitis.[7] Other virus encephalitides have only recently become diagnosable by special tests. Indeed, the diagnosis of mumps meningoencephalitis may, at times, be extremely difficult to make: "The diagnosis depends upon the development of meningitis, deafness, or other neurological syndromes . . . during or within a few weeks after the attack of mumps. . . . If the child develops such symptoms without parotitis, it scarcely seems possible to establish the diagnosis with certainty. . . ."[32]

In the following case, which we wish to report, there was no history of exposure to mumps, no current epidemic of mumps, and no development of parotitis at any time, all of which would have been important diagnostic clues.

CASE REPORT

Chief Complaint.—Lethargy, abdominal pain, and vomiting, of 24 hours' duration.

Past History.—The patient was born Nov. 5, 1937, following a normal pregnancy. Delivery was complicated by a late prolapse of the cord, but the child appeared healthy at birth, and his subsequent growth and development were normal. He had had no illnesses except measles and chickenpox at the age of 7: he specifically had not had mumps. To the parents' knowledge he had not recently been exposed to any contagious disease.

Family History.—The patient's family consisted of his parents and a sister, aged 10, all of them apparently well. There were no familial diseases.

Present History.—On December 15, two days prior to hospital entry, the patient complained to his mother that the base of his nose hurt considerably. The mother saw nothing wrong with it, but gave him some nose drops, which relieved his symptoms. He seemed perfectly well the rest of the day and the next morning, when he went off to school; however, he returned at noontime saying that he was "sick." He complained of a dull frontal headache, generalized abdominal pain, and tiredness. He went to bed and slept most of the day, refusing to eat anything because of nausea, and promptly vomiting any fluids forced upon him. He seemed feverish but his temperature was not taken. The next morning, December 17, he was very lethargic and had an oral temperature of 102° F., which prompted the mother to bring him to the hospital. A system review was otherwise negative.

Physical Examination.—The patient was admitted to the isolation ward vomiting, with an oral temperature of 101° F., a pulse rate of 96, and a respiratory rate of 26. He appeared acutely ill and dehydrated. His skin was somewhat hyperkeratotic and there was slight circumoral pallor, but no evidence of a rash. Examination of the ears, nose, and throat was negative. The lips were parched and the tongue heavily coated. Both parotid duct orifices appeared questionably puffy and injected. There was no parotid tenderness or swelling. The neck was slightly stiff, so that the patient could not quite touch his chin to his chest; any attempt at forced forward flexion of the neck caused him to complain of increased abdominal pain, which he could not well describe. There was no appreciable cervical or other lymphadenopathy. The lungs were clear to examination. The heart size was normal to percussion, the cardiac rate 96, and the rhythm regular; there was a soft systolic murmur heard equally well at the apex and in the second right interspace, not transmitted, and varying in intensity with change of position. Examination of the abdomen was negative except for slight tenderness, diffuse over the whole left abdomen, without local spasm or rebound tenderness. Gross examination of the genitourinary, muscular, and bony systems was negative. All reflexes tested were normal and no pathologic ones were elicitable.

Entry Laboratory Findings.—A white count taken on admission was 8,200 with 90 per cent neutrophiles and 10 per cent lymphocytes. A urinalysis was negative. A chest x-ray on admission was negative.

Entry Clinical Impression.—(1) Acute gastroenteritis, with dehydration and meningismus; and (2) functional heart murmur were the clinical impression.

Clinical Course.—Approximately five hours after entry, the patient became rather suddenly semicomatose. Examination at this time revealed an oral temperature of 101.6° F., somnolence, increased nuchal rigidity, and unsustained bilateral ankle clonus, but was otherwise as on admission. A spinal puncture was then performed and a clear, crystalline fluid under normal tension obtained, containing 191 cells (84 per cent lymphocytes and 16 per cent neutrophiles) and a total protein of 90 mg. per cent. No bacteria were seen on direct smear. Aerobic and anaerobic cultures were negative at the end of four days. Spinal fluid sugar and chloride levels were not done.

Although this did not appear to be a bacterial infection, the patient was begun on intramuscular penicillin. For the first two days he remained very lethargic, arousable and oriented, but "dopey." He continued to vomit everything offered by mouth and was maintained on intravenous infusions of glucose, saline, and plasma. His temperature remained at 101° F., the first day, varied between 99.8° and 101° F. the second day, slowly returned to normal the third day, and remained so thereafter. His pulse rate and respiratory rate were never appreciably elevated.

On the third hospital day the patient's condition improved quite dramatically: he felt comfortable, ate well, and was normally alert. Physical examination at this time was entirely negative. His white count on the third day was 7,600, with 48 per cent neutrophiles and 52 per cent lymphocytes. Because of his apparently spontaneous and sustained recovery the penicillin was stopped on the fourth day, and he was allowed to go home on the fifth day, as his parents desired. His convalescence at home was brief and complete. At no time there or in the hospital did he have signs of, or symptoms referable to, a parotitis.

Remarks.—

1. Because of a nursing shortage, it has been necessary for the mother of a child admitted to the isolation ward of this hospital to remain with the child day and night, sleeping in the same room. Accordingly, this patient's mother was in the closest possible contact with him throughout his illness.

2. On Dec. 28, 1946, the patient's sister, aged 10, was admitted to the hospital complaining of a dull pain beneath the lobe of the left ear, which she had had for three days and which was aggravated by chewing food. On entry her temperature was 101.6° F. She did not appear very ill in spite of her fever. Physical examination was negative except for a small area of redness over the tip of the left mastoid and marked tenderness beneath the lobe of the left ear, to palpation and on speculum examination of the left auditory canal. Her white-cell count was 8,200 (neutrophiles 64 per cent, lymphocytes 36 per cent). Because of the possibility of this being a mastoiditis, she was given both oral sulfadiazine and intramuscular penicillin, neither of which seemed to have any effect. She continued to complain of pain on the left side for one to two days, then pain in the same area on the right side of her face for two more days. Her "spiking" fever lasted four days, after which she had no symptoms. Her white-cell counts remained normal throughout. At no time did she have an evident parotitis.

3. On Dec. 31, 1946, fifteen days after the onset of the boy's illness and six days after the onset of the girl's illness, the mother of these two children noticed a painful swelling of her face, which had become a full-blown bilateral parotitis by the time she was seen in the outpatient clinic that afternoon.

DISCUSSION

In the 280 cases of mumps meningoencephalitis which we were able to find, there were thirty-six which occurred without apparent parotitis, an incidence of 13 per cent. In all except those reported by Enders and his associates,[23] the diagnosis was based on the typical clinical picture appearing either during an epidemic of mumps or in individuals with a definite history of ex-

posure to mumps. In the case reported here, there was no epidemic or history of exposure to suggest the true diagnosis. Nor could the illness of the patient's sister be called a case of mumps with any certainty, which might have suggested, albeit rather late, the cause of the boy's illness. Yet both the boy and his sister, five to six weeks after their recovery, had high (1:502) complement fixation titers for the mumps virus,* so there can be little doubt that both were cases of mumps virus infection. The girl's illness would seem to be a good example of atypical or unsuspected mumps, the type of infection which Enders[33] has stressed.

This case of meningoencephalitis suggests that the disease without parotitis is infectious, for it seems certain that the mother, who was in the closest possible contact with the patient throughout his illness and who developed mumps parotitis fifteen days later, caught the disease from him. It resembles Jersild's Case XIII,[19] a girl who developed meningitis but no parotitis shortly after coming into an isolated region from an epidemic area, and who apparently infected two other children, both of whom came down with classical mumps fifteen days later. Jersild felt that this sequence proved the etiology of the meningoencephalitis, but in cases without parotitis, such as his and ours, the complement fixation test may be the only way to make the diagnosis with certainty. It, therefore, seems reasonable to expect that the wider clinical use of this test in the future will disclose many cases of meningoencephalitis, otherwise unprovable, to be due to mumps, and thus make even more obvious the fact that the disease is more common than most physicians realize.

SUMMARY

1. From the literature, 280 cases of mumps meningoencephalitis have been collected, to describe the clinical picture of the disease.

2. A case of mumps meningoencephalitis without parotitis, here reported, serves to emphasize both the difficulty in diagnosing an occasional case and the value of the complement fixation test as a diagnostic procedure.†

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†This article expresses the opinions of the authors and does not necessarily represent the views of the Army Medical Department.

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File Pneumonia – Friedländers

FRIEDLÄNDER'S PNEUMONIA IN INFANCY

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THE rarity of pneumonia caused by *Klebsiella pneumoniae* in infancy and childhood is best expressed by Julianelle,[1] who has made an extensive study of the subject. He states, "The writer has never seen an example of this pulmonary disease in infants or children, and the scarcity of references in the literature illustrates clearly its extreme rarity in the lower age groups."

There has been a total of four cases of primary *K. pneumoniae* (Friedländer's bacillus or *Bacillus mucosus capsulatus*) pneumonia reported up to the present time. To these we are adding our case, for a total of five. Comba (as quoted by Collins[2] and by Ferguson and Tower[4]) reported a fatal case in a 6-day-old infant in Italy in 1896. In 1915, Dunn and Hammond[3] reported a case in a 14½-month-old infant with spontaneous recovery. Simultaneous cases in 7-month-old twins with the death of one and the survival of the other were reported in 1933 by Ferguson and Tower.[4] For the sake of completeness, two additional cases may be included, although the disease in both cases was secondary to *K. pneumoniae* enteritis in the terminal phase. Both of these were included in a report by Jampolis and associates[5] from Michael Reese Hospital.

While it has been customary for years for writers to refer to a characteristic sputum in Friedländer's pneumonia as a differential point from pneumococcus pneumonia, more recently students of the subject find that the diagnosis is a purely bacteriologic one so far as the lobar form is involved. Indeed, as Julianelle[1] succinctly states, the report from the laboratory usually comes as something of a surprise. Besides the lobar form, which is indistinguishable clinically and radiographically from pneumococcus pneumonia, there is a chronic form which closely simulates chronic pulmonary tuberculosis. The chronic form may have a slow and insidious onset, or it may be a sequel to the lobar form. In the chronic form, the changes in the lung consist of necrosis and abscess formation, sloughing and cavitation, and finally, if healing sets in, fibrosis. The cavities are said to be particularly thin-walled. Collins[2] also emphasizes the resemblance between chronic Friedländer's pneumonia and chronic pulmonary tuberculosis. The peculiar predilection of this disease for persons in the fourth and fifth decades of life is reported universally. Reference to Hyde and Hyde[6] and Julianelle[1] will provide a fuller discussion of the subject. The fatality rate of the untreated disease is very high, with most responsible investigators reporting rates in excess of 80 per cent. Bullowa and Perlman,[7] and Hyde and Hyde,[6] among others, have commented upon the ineffectiveness of the sulfonamide drugs in the treatment of Klebsiella infections of the lung.

From the Pediatric Service of Dr. Harry S. Altman and the Radiologic Service of Dr. Ernst Kraft, Lincoln Hospital.

REPORT OF A CASE

A male child was born Jan. 17, 1947, by low forceps delivery from the left occipitoanterior position. A true knot was found in the cord, which was wound once around the infant's neck. The child was apneic at birth and required nine minutes of artificial respiration before spontaneous respirations became apparent. Coramine was given in a dose of 0.5 c.c. The child was sent to the nursery in fair condition after observation for one hour in the delivery room. Birth weight was 5 pounds, 8 ounces.

The child was first seen by the Pediatric Service on January 20, when consultation was requested by the Obstetrical Service because of the child's failure to recuperate properly from his initial stormy episode. At this time, the baby's weight was 4 pounds, 14 ounces. There was evidence of dehydration, inanition, and widespread atelectasis. Continuous oxygen therapy had been maintained and was continued. Clyses were given and the child was taken off the breast and placed on small, three-hourly feedings of stock formula. In general, the baby did not make much progress, was cyanotic much of the time, and had a constant, profuse, thick, yellow, mucoid discharge from the nose and throat, which necessitated frequent suction to maintain a patent airway. The sole encouraging feature about the patient was that he slowly regained some of the initial weight loss, with a body weight of 5 pounds, 2 ounces on January 30.

On February 5, fine, moist, inspiratory râles were heard in the right and left lung fields. Treatment with intramuscular penicillin, 20,000 units immediately and 10,000 units every three hours, and oral sulfadiazine, 0.16 Gm. immediately and 0.078 Gm. every four hours, was instituted. An x-ray of the chest on that day revealed irregular clouding of both upper lung fields and round areas of diffuse density in the right middle and left lower lung fields. There were 16,000 leucocytes per c. mm., of which 42 per cent were polymorphonuclear. Lumbar puncture on February 6 was productive of spinal fluid normal in every respect.

The patient's temperature reached 100.4° F. on February 8, the first noted elevation. By February 10, positive physical signs could no longer be found in the chest and the specific therapy was discontinued. Repeated examination of the urine had been negative. A blood Kline test was also reported negative.

The baby's course continued to be stormy. The body weight on February 11 was 4 pounds, twelve ounces. X-ray examination of the chest on February 13 showed an increase in the size of the previously noted round densities. Their exact nature was not apparent. On February 15, he was given a transfusion of 30 c.c. of whole blood. The patient weighed 5 pounds, 4 ounces on February 19, but he began to run a low-grade fever. By February 23, the fever had become marked and signs of massive consolidation involving the entire left lung were obvious. The administration of penicillin and sulfadiazine was begun in the same dosage as previously used, continuous oxygen was given, and caffeine-

sodium-benzoate was injected subcutaneously at frequent intervals. The blood hemoglobin at this time was 13.5 Gm. per 100 c.c. and there were 18,200 leucocytes per c. m.m. of which 62 per cent were polymorphonuclear. X-ray examination of the chest confirmed the diagnosis of "lobar" pneumonia of the left lung. There was no response to therapy. By the morning of February 27, the infant's temperature had risen to 104.8° F. and the child appeared moribund. At this time, both the nose and throat cultures taken prior to the institution of therapy were reported as showing *K. pneumoniae* (Friedländer's bacillus). The use of penicillin and sulfadiazine was stopped and the child was immediately started on streptomycin. The dose of the latter antibiotic was 0.67 Gm. daily in eight divided doses, using the intramuscular route. An unexplained finding on the following day was a tendency toward opisthotonos.

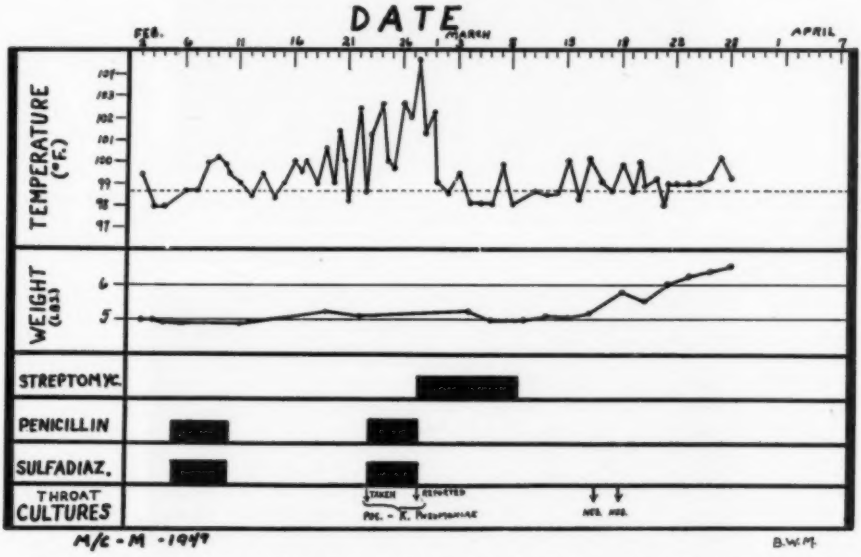

Chart 1.—Course of the patient through the period of infection and early convalescence.

Lumbar puncture was done, but the spinal fluid was again found to be completely normal. By March 1, after two days of streptomycin therapy, the baby's clinical condition was considerably improved and the temperature had rapidly fallen to normal. Because of his poor state of nutrition, the patient was given 60 c.c. of pooled plasma intravenously. From this date the child made a steady improvement, appearing stronger and more alert with each passing day. Radiographic examination of the chest on March 6 showed considerable clearing of the previously noted densities, particularly in the left lung field. Concentrated feedings were started on the same day. On March 8, after having been afebrile for eight days and on streptomycin therapy for ten days, the patient's antibiotic was discontinued.

Fig. 1.—Feb. 13, 1947: rounded areas of pneumonic consolidation in both lung fields which are larger than in typical bronchopneumonia.

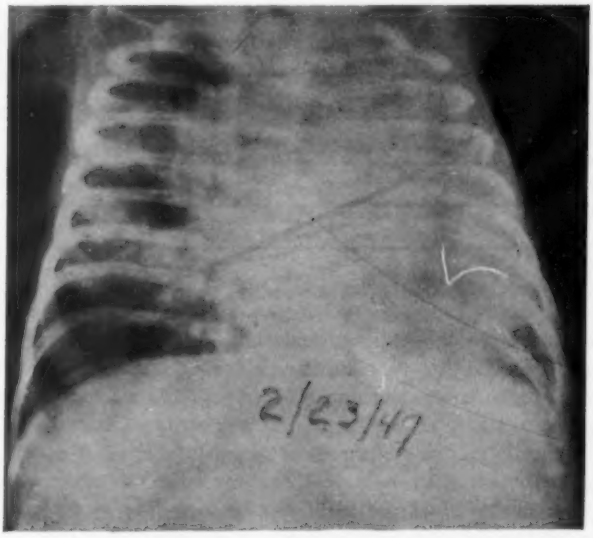

Fig. 2.—Feb. 23, 1947: pneumonic consodilation of the entire left lung field (pseudolobar consolidation) due to coalescence of smaller areas of consolidation, blotchy areas of consolidation throughout the right lung field.

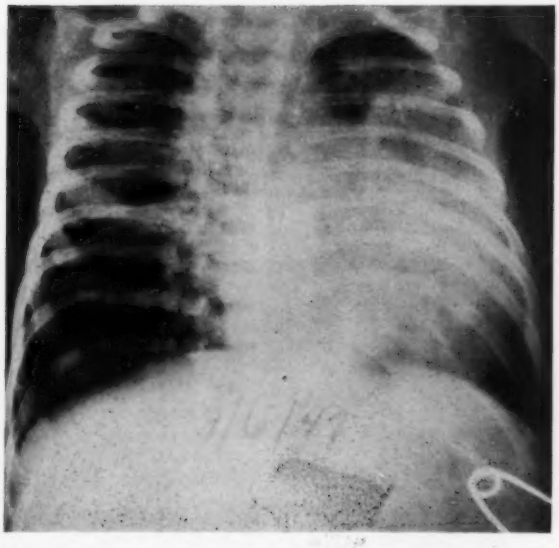

Fig. 3.—March 6, 1947: moderate clearing of the pneumonic consolidation in the left lung field with an area of decreased density due to cavity formation in the left upper lung field, and clearing of the consolidation in the right lung field with the appearance of cavity formation in the upper portion of the lung.

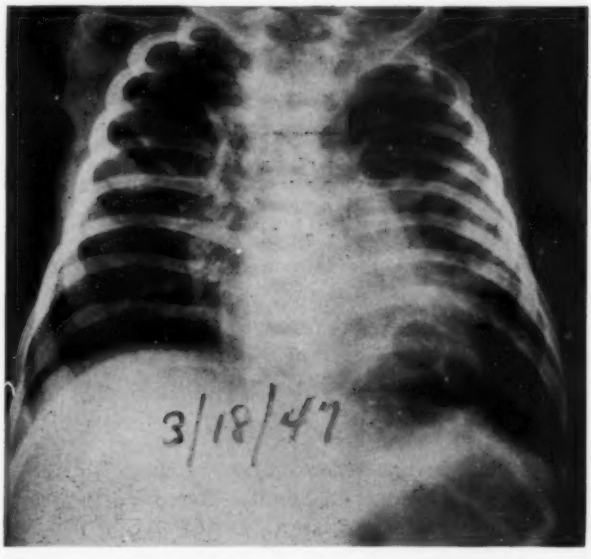

Fig. 4.—March 18, 1947: further clearing of the consolidation in the left lung field with the appearance of several thin-walled cavities in the lower portion. The cavity in the right upper lung field is now larger than on the preceding film.

A definite weight gain was noted by March 15. On March 22 the patient weighed 6 pounds and the course was now definitely uphill.

Beginning with an x-ray of the chest on March 18, cystic changes were noted in the right upper and left lower lung fields. The changes became even more pronounced by March 28. The lesions had the appearance of cavities, devoid of fluid content and with fairly thin walls. Occasional moist râles could still be heard over the left lung field. These were interpreted as being part of the picture of resolving pneumonia.

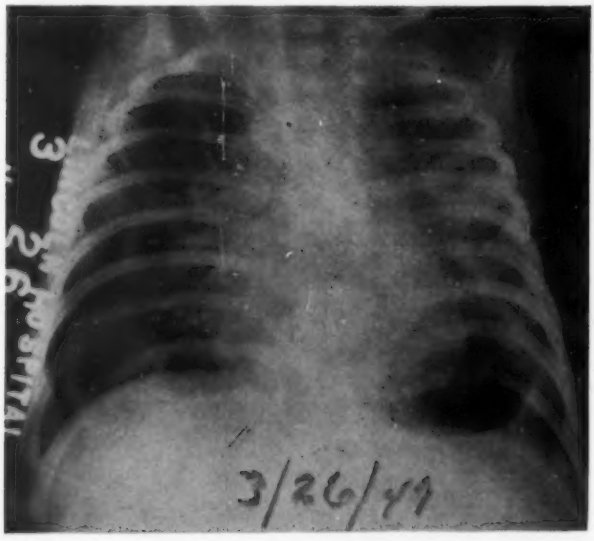

Fig. 5.—March 26, 1947: coalescence of several cavities at the left base to form one large, thin-walled cavity. The cavity in the right upper lung field is now larger than on previous examinations.

Nose and throat cultures taken on March 16, 18, and 29 failed to grow *K. pneumoniae*. On April 9, the baby weighed 7 pounds and 6 ounces and showed no evidence of disease other than the persistence of the "cavities" in the chest on follow-up radiographic examinations. A Mantoux test done on April 16 was negative. The patient was discharged from the hospital on April 23, 1947, weighing 8 pounds, 4 ounces, and appearing to be in the best of health.

COMMENT

The case presented in this report illustrates classically the course of the disease as it has been described in adults. Reference to the accompanying chart of the clinical course and to the serial radiographs of the chest cannot fail to impress one with the insidious onset of the infection, the therapeutic failure of sulfadiazine and penicillin, and with the rapidity of the response to treatment with streptomycin. While cases such as this admittedly are rare in in-

fants and children, still they can and do occur. We are convinced that were cultures taken from every case of pneumonia in infancy, more cases would be recognized. In this day of an increasing variety of antibiotic agents, each with its own *selective* activity, it becomes increasingly more important that such cultures be taken. Until such time when there may be available a panacea for all infections, specific therapeusis will require specific etiologic diagnosis.

SUMMARY

A case of *K. pneumoniae* pneumonia in a newborn child has been presented. Recovery with streptomycin therapy was dramatic following the signal failure of both sulfadiazine and penicillin to control the infection.

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PREMATURE CLOSURE OF THE CRANIAL SUTURES

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CRANIOSTENOSIS is a relatively rare anomaly in which the sutures of the skull close prematurely, causing compression of the intracranial contents. Many variations of this anomaly occur, depending upon which sutures close prematurely, and also depending upon what other anomalies may be associated with the craniostenosis. This variability in the clinical picture has resulted in a poor understanding of craniostenosis. Therefore, in this report, in addition to discussing the types of craniostenosis, we shall classify the various forms of this condition in a manner which we hope will eliminate some of the confusion which now exists.

Although the surgical treatment of craniostenosis is not new, there is still little uniformity of opinion as to what operations should be employed in the treatment of this anomaly, and some authors still express doubt as to the efficacy of any type of operation. This lack of confidence in surgical intervention is not without basis. There have been few reports of long-term successful results following operation.

It is probable that the surgical results might be more satisfactory if the indications for such operations were better understood, and if for each case an appropriate operative procedure were adopted. Since suitable operations do not seem to have been utilized in all reported cases, the various surgical procedures which have been suggested for the treatment of craniostenosis are reviewed and, in addition, a modified operative procedure is described. This modification for the prevention of bony regeneration across the newly made skull defects should be effective in eliminating one of the chief causes of poor results following craniectomy for craniostenosis.

Reports in the literature of patients with craniostenosis who have been operated upon are not numerous, and for this reason, reports on five additional cases illustrating many typical problems would seem to be of value.

HISTORY

In 1851 Virchow[1] first described the relationship between premature closure of the cranial sutures and the distressing symptoms which result from such closure. To this condition he gave the name craniostenosis. In 1855, MacKenzie,[2] in his textbook on ophthalmology, reported that there were certain cases of "hydrocephalus" in which the skull height was increased and the orbits were found to be shallow, and that in these cases exophthalmos and blindness occurred. From his description there can be little doubt that he was

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dealing with cases of premature closure of the cranial sutures rather than with hydrocephalus. Von Graefe,[3] in an article on neuroretinitis written in 1866, described the case of an 8-year-old boy who had a very high, narrow head, visual impairment, epilepsy, exophthalmos, and papilledema. Von Graefe suggested that the papilledema was due to increased intracranial pressure secondary to the skull deformity. He was the first to recognize the importance of visual impairment in craniostenosis. Following this paper by von Graefe, many case reports of this anomaly were published, especially in the German literature, but there was a tendency at that time to confuse craniostenosis with microcephaly. It was not until after roentgenography was introduced that these two anomalies were separated with any degree of accuracy.

In 1890, Lannelongue[4] published the first report of an attempt to relieve the symptoms of this disease by removing strips of bone along the prematurely synostosed sutures which would allow for expansion of the skull. In 1892, Lane[5] reported two patients upon whom he had done linear craniectomies. In 1894, Jacobi[6] was able to find reports of thirty-three patients upon whom operations had been performed to relieve craniostenosis, but he severely criticized operations to correct cranial deformities. He pointed out that while there might be some justification for operation on those patients who had a true premature synostosis of the cranial sutures, most of these operations were being done on true microcephalics on whom an erroneous diagnosis of craniostenosis had been made.

In the last fifty years, there has been published an extensive literature relative to craniostenosis, and during this period much has been learned concerning this anomaly, but a great deal of confusion still exists concerning the etiology, symptoms, classification, and treatment of craniostenosis. In more recent years there has been a revival of interest in the surgical treatment of this condition, and several new operations have been suggested for its treatment.

NORMAL SKULL GROWTH

There is commonly a slight separation of the cranial bones at birth, but a firm, fibrous union is present by the end of the fifth or sixth month. By the end of the sixth week the posterior and lateral fontanelles are obliterated, and normal closure of the anterior fontanelle occurs between the tenth and sixteenth months.

Normal growth of the skull and obliteration of the sutures of the skull are directly dependent upon normal brain growth. In microcephaly there are commonly premature obliteration of the fontanelles and premature closure of the sutures. In hydrocephalus, on the other hand, obliteration of the fontanelles and closure of the sutures are delayed. Further evidence that growth of the skull is directly dependent upon brain growth is shown by the fact that in cases in which there is atrophy or lack of growth in one cerebral hemisphere in early childhood, the corresponding side of the skull is smaller than on the normal side. Growth of the brain has been demonstrated by Scammon and Dunn[7] to form a parabolic curve when plotted graphically, the period of rapid

growth lasting for only the first two to three years. Since the growth of the cranium is dependent upon the growth of the brain, the rate of growth of the skull parallels the rate of growth of the brain. After the age of 3 years there is only a slight increase in intracranial capacity, and any increase in the head size is due largely to thickening of the bones of the skull and growth of the accessory sinuses and the bones of the face.

Giblin and Alley[8, 9] believe that skull growth occurs in two ways. First, growth occurs by accretion of bone on the external, convex surface of the skull, with simultaneous resorption of bone from the inner, concave surface. Growth also occurs in a lateral direction from the sutures of the skull. Giblin and Alley have demonstrated experimentally that this lateral growth from the sutures does occur. Troitzky[10] has demonstrated experimentally that growth of the cranial bones in a lateral direction is from the suture lines and that there is no interstitial growth of the bones of the skull. This experimental observation is corroborated by the clinical impression that following synostosis of a suture, no growth takes place in a direction perpendicular to that suture. Giblin and Alley have shown that in experimental animals the cranial sutures will fuse if normal movement of these sutures is stopped by placing a single bridge of bone across the suture line. Thus we see that even in normal skulls synostosis of a suture, once it starts, may tend to extend until the suture is completely obliterated. Bolk[11] has shown that the sutures may be completely obliterated in what appear to be perfectly normal skulls at a much earlier age than is usually considered normal. In a study of 1,820 skulls of individuals who were from 3 to 20 years of age, he found a synostosis of one or more sutures in 343 of the skulls. Greig,[12] in his discussion of oxycephaly, classified certain cases of premature closure of some of the cranial sutures without deformity as false oxycephaly. Apparently these cases of false oxycephaly of Greig and the premature closure of cranial suture described by Bolk are the same. It seems unwise to use the term "false oxycephaly" to describe what apparently is a normal variation of skull growth inasmuch as the term suggests a pathologic condition. Bolk believes that when this premature synostosis occurs, it usually does so between the ages of 4 and 6 years, because the percentage of incidence of premature obliteration of the sutures remains constant after the sixth year. This early physiologic closure of the cranial sutures occurs, then, at a time when the brain has practically attained its adult size, and it is probably for this reason that no symptoms result in these patients.

CLASSIFICATION OF PREMATURE SYNOSTOSIS

One of the chief difficulties in arriving at a clear understanding of premature closure of the cranial sutures is the complex descriptive terminology which has accumulated. The terminology is confusing because different names have been applied to identical forms of the anomaly and also because many superfluous subdivisions have been made to separate minor variants.

Some of the terms used to describe this anomaly are: premature synostosis, synostosis cranii, craniostenosis, oxycephaly, delayed oxycephaly, false oxycephaly, pyragocephaly, turricephaly, turmschadel, steeple-skull, turret-skull,

sugar-loaf skull, scaphocephaly, plagiocephaly, clinocephaly, trigonocephaly, leptocephaly, acrocephaly, craniofacial dysostosis of Crouzon, and acrocephalosyndactylism.

To add to the confusion of this complicated terminology, some investigators would separate and classify as entirely different types of cranial deformity, types, which, in reality, should be classified as variants of craniostenosis. Thus Greig,[12] for example, believes that oxycephaly is a disease process distinct from the other forms of premature synostosis of the cranial sutures because he believes that in oxycephaly true suture lines are never developed. Sear,[13] on the other hand, states that he has observed occasional cases of severe oxycephaly in which certain of the suture lines remained open. This difference of opinion may be due to the fact that Greig was studying museum skulls, while Sear's observations were made on clinical cases. Our experience with a case of severe oxycephaly (Case 2) is in agreement with Sear's observations. In this case the frontonasal and spheno-occipital sutures could be demonstrated on roentgenographic examination to be open in spite of the severity of the oxycephaly (Figs. 1 and 2). Whereas it is true that the oxycephalic skull has a shape which is distinctly different from those found in other forms of craniostenosis, there does not appear to be sufficient evidence to indicate that it is a different disease process. In fact, there is considerable evidence to prove that oxycephaly is closely related to the other types of craniostenosis. It has been observed frequently that other members of a family in which there is a member with typical well-advanced oxycephaly, may have skulls which are definitely abnormal but not oxycephalic. The deformities commonly associated with oxycephaly are also found associated with other forms of craniostenosis. Cases of oxycephaly are seen in which the sutures are present early, and when the sutures close, the skull assumes a typical oxycephalic shape. Greig[12] refers to these as cases of delayed oxycephaly, a process which he considers as unrelated to true oxycephaly. All forms of premature synostosis of the cranial sutures are, in his report, considered to be merely variants of a single disease process. This concept is not new. Bertolotti,[14] in 1914, suggested that all these deformities be grouped together and called the cranial dystrophies. Sear[13] was also of the opinion that all of these deformities should be considered as a single anatomopathologic entity.

A simple, workable classification can be made by eliminating duplications in terminology and by disregarding the minor variations, which are probably of little significance. The following classification seems to be reasonably simple, and yet it separates the important groups making up this condition.

A. Complete, early, premature synostosis of the cranial sutures (oxycephaly, turrecephaly, turmschadel).
   1. Oxycephaly without facial deformity.
   2. Craniofacial dysostosis of Crouzon.
   3. Acrocephalosyndactylism.
   4. Delayed oxycephaly (onset after birth).

B. Incomplete early synostosis of the cranial sutures.
   1. Scaphocephaly: premature closure of the sagittal suture.
   2. Brachycephaly: premature closure of the coronal suture, or of the coronal and lambdoidal sutures.
   3. Plagiocephaly: asymmetrical premature closure of the sutures.
   4. Mixed.

C. Late premature synostosis of the cranial sutures after the skull has reached or nearly reached adult size so that no deformities and no symptoms result. (This is included only to show its relation to true craniostenosis and to make it clear that surgical treatment is not indicated. This process should not be considered pathologic.)

Fig. 1.—(Case 2.) Postoperative roentgenogram showing the spheno-occipital suture to be open despite a severe degree of oxycephaly.

ETIOLOGY

The etiology of craniostenosis is not known, but many possible causes have been suggested. Virchow,[1] in his original description of the anomaly in 1851, suggested that premature synostosis might follow inflammation of the meninges. Others have suggested that intrauterine meningitis might be the etiologic agent. Rickets, syphilis, glandular dysfunction, and birth trauma have all been mentioned as possible causes. Young,[15] in studying two cases of oxycephaly, found the blood calcium levels to be 18 mg. per cent in one and 20 mg. per cent in the other. Because of these findings he suggested that the anomaly was due to some inherent defect in the germ plasm rather than to any mechanical fac-

tors. There is some evidence to substantiate this point of view. There is no doubt that at least in certain instances the anomaly is familial and also craniostenosis is frequently associated with other congenital defects.

Greig[12] and Ogilive and Posel[17] have suggested that the development of craniostenosis may be related to disturbances in growth of the sphenoid. Ogilive and Posel, in studying a case of scaphocephaly, found that the greater wings of the sphenoid were small, and the lesser wings were larger than normal, but the reverse was true in cases of oxycephaly, the greater wings of the sphenoid being much larger than normal. They felt that this enlargement of the greater wings of the sphenoid probably accounted for the wide skull, temporal bulging, and shallow orbits, abnormalities which are present with oxycephaly.

Fig. 2.—(Case 2.) Roentgenogram showing the open frontonasal suture.

Mann,[18] in discussing the development of oxycephaly, stated that there was failure of normal growth of the lateral portions of the base of the skull which develop from the visceral mesoderm of the first visceral arch. On the other hand, he felt that the central portion of the base of the skull which arises from the periaxial mesoderm develops normally.

Morselli,[19] Rieping,[20] and Sear[13] have suggested that premature synostosis of the cranial sutures is due to the centers of ossification in the adjacent bones being in too close proximity. Rieping[20] thought that there was, in addition, some fault in the blastodermal matrix separating the bones. Giblin and Alley[8] have shown in experimental animals that synostosis of the cranial sutures is influenced by the mobility of the bones when they demonstrated that synostosis of a suture will occur if the bones are immobilized by a bony bridge across the suture. This being true, a premature synostosis may be self-perpetuating once it starts.

It has long been recognized that heredity might be an important factor in the etiology of the anomaly, and the hereditary or familial tendency of craniostenosis is shown by numerous reports of this process occurring in siblings or in succeeding generations in the same family.[17, 21-29] The mother of one of our patients with craniofacial dysostosis (Case 2) had a high narrow head, hypertelorism, divergent strabismus, and prognathism. Gunther,[30] in a review of the literature on oxycephaly, found in several pairs of twins a typical oxycephalic deformity occurring in both.

SYMPTOMS

Premature closure of the cranial sutures occurs much more commonly in males than in females. Sharpe[31] has stated that males are affected five times as frequently as females.

It is apparent that the severity of the skull deformity and of the other symptoms resulting from premature synostosis depends not only upon which sutures are obliterated but also upon the age at which this synostosis occurs, a severe degree of deformity occurring only if the process begins early in life. It is probable that no symptoms will occur if synostosis of the cranial sutures begins after the age of 3 years. As has been stated previously, these cases which begin after the age of 3 should probably be classified as a variation of normal skull growth rather than a pathologic premature closure of the sutures. Although mild deformity of the skull may result, these cases probably never need treatment.

All cases of premature synostosis have abnormally shaped heads, the shape depending upon which sutures are prematurely closed, and also in what order they close. If the sagittal suture closes, dolichocephaly results; but if the coronal sutures close, the head becomes brachycephalic. Closure of the sutures on one side will cause an asymmetry of the skull, and closure of all of the sutures will cause the skull to be tower shaped because of the pressure upward against the open anterior fontanelle by the brain, which is still expanding.

Because the change in the shape of the skull from normal to definitely abnormal is very gradual, the parents usually do not realize that a pathologic process is present until the deformity is far advanced. However, frequent observations by a physician may establish the diagnosis at an early stage of the condition, especially if head measurements are taken routinely. Early recognition is of the greatest importance, since the results of surgical treatment in the anomaly depends in a large measure upon the promptness with which surgical intervention is initiated.

Certain other abnormalities of the skeletal system are commonly associated with premature synostosis of the cranial sutures. There may be shallow orbits resulting in exophthalmos. Premature synostosis of the sutures of the facial bones may occur, resulting in the typical facial appearance described by Crouzon[24] and characterized by exophthalmos, divergent strabismus, a saddle-shaped nose, decreased prominence of the maxillary processes, a prognathous jaw, a very high arched palate, and dental abnormalities due to the small

maxilla. Many, especially the oxycephalic variety, have a divergent strabismus and increased distance between the eyes as described in 1924 by Greig[32] when he reported two patients presenting this deformity and suggested it be called hypertelorism. Neither of Greig's patients, however, had a premature closure of the cranial sutures. He had the opportunity to examine the skull of one of these, and from his examination he concluded that the deformity was caused by an exaggerated growth of the lesser wing of the sphenoid, whereas the greater wing remained smaller than normal. Greig felt that hypertelorism should be considered an entirely separate type of craniofacial deformity rather than a form of craniostenosis. Hypertelorism may be seen not only in cases of craniostenosis, but also in association with other conditions, or it may even be an isolated finding. Braithwaite[33] has reported a case of hypertelorism in a Mongol. Hypertelorism is an excellent descriptive term and should be retained for this condition, but it is doubtful if hypertelorism should be considered an entirely separate anomaly.

Syndactylism associated with oxycephaly was first described by Wheaton[34] in 1894, and since that time others have also discussed this syndrome and applied to it the name acrocephalosyndactylism. The syndactylism may affect either the hands or the feet, and it may be associated with other congenital anomalies in the bones of the extremities. Some authors believe that acrocephalosyndactylism should be considered a separate anomaly rather than a form of craniostenosis with associated anomalies. As in the case of hypertelorism, it is more probable that this syndrome is one of the variants of craniostenosis rather than a separate anomalous process. Many other congenital deformities, including nevi, mongolism, harelip, hypoplasia of the genitalia, pituitary dysfunction, kyphosis, spina bifida, genu valgum, pes planus, osteogenesis imperfecta, hydrocephalus, and hemolytic icterus, have been reported associated with premature closure of the cranial sutures.

Except for deformity of the skull itself, the most common symptoms of craniostenosis are those related to the eyes. For this reason much of the early writing on this disease is to be found in the ophthalmologic literature, and even now many of these cases are seen first by the ophthalmologist.

Exophthalmos is a common symptom, and is due to a shallow orbit which results from the orbital roofs being more vertical than normal. External strabismus is commonly associated with the exophthalmos, the external strabismus being due to the fact that the orbital axes assume a downward and outward direction. At times the exophthalmos may be of such severe degree that the lids cannot be closed, and corneal ulceration occurs.

Loss of vision due to optic atrophy is frequently found in craniostenosis of severe degree. Gunther,[30] in reviewing the literature, found that sixty-seven of a total of seventy-four patients had optic atrophy. Several theories have been proposed to account for the atrophy. Schloffer[37] and Van der Hoeve[38] have suggested that the optic foramina are smaller than normal, and that the pressure on the optic nerves by the walls of the constricted foramina causes optic atrophy and blindness. Behr[39] and Beaumont[40] believe that the atrophy

is due to an angulation of the optic nerve caused by the combination of a deep middle cranial fossa and an orbital roof which assumes nearly a vertical plane resulting in an overhanging superior rim of the optic foramen. This angulation causes the optic nerve to be compressed between this overhanging roof of the optic foramen and the pulsating internal carotid artery below. The most commonly accepted theory is that the blindness is secondary to papilledema associated with generalized increased intracranial pressure. Bennett and coworkers[41] have found intracranial pressures ranging as high as 80 mm. of mercury, and Gunther[30] has reported cases having pressures of 450 mm. of water. Papilledema is commonly seen in severe cases and one would expect that optic atrophy would follow on this basis alone, especially since the increased intracranial pressure is of long duration. There have been reports of cases in which papilledema occurred in adulthood long after the brain had reached its adult size. It is difficult to explain the occurrences of papilledema in these adult patients who apparently have had no previous evidence of increased intracranial pressure.

Convulsive seizures frequently occur in craniostenosis but usually have their onset late in the course of the disease.

There is still a difference of opinion among investigators as to the mental status of these patients. Many authors, even in recent years, have insisted that the disease is not necessarily associated with mental deficiency, and many cases have been reported to confirm this opinion. Some have said that these patients may even be of superior intelligence. Obviously, one reason for such statements is that these authors were including cases in which there was a late development of premature closure of the sutures, cases which may have no symptoms, and as previously stated, these cases should not be considered as pathologic.

So many of the reported cases of craniostenosis have been associated with mental deficiency that there seems to be no question but that the two are concomitant. While the literature presents many cases of true craniostenosis in which the authors stated that the mentality was normal, it is apparent that most of these statements were based on casual observations of the patient without psychological testing to give an accurate measure of the intelligence. In reviewing the literature on this disease, only one case was found in which it was quite evident that the patient's intelligence was above normal. This patient was one of the cases of Faber and Towne[42, 43] upon whom a linear craniectomy had been performed. Since this patient had good growth of the skull following the operative procedure, he cannot be considered as showing the usual symptoms of a patient with craniostenosis.

ROENTGENOGRAPHIC FINDINGS

In all cases of premature synostosis of the cranial sutures, the obliteration of the sutures can be most readily demonstrated on roentgenographic examination. The bone immediately adjacent to the obliterated suture shows an increased density and is of greater thickness here than elsewhere in the skull.

The characteristic shape of the skull, depending upon which sutures have been prematurely synostosed, is readily apparent in the roentgenogram. In fact, the abnormal shape of the skull is frequently more apparent on roentgenographic examination than on physical examination. Especially is this true in older children and in adults in whom the hair hides the characteristic deformity. In addition to abnormalities in the sutures and shape of the skull, certain other associated changes are frequently visible in the roentgenogram. The orbits may be shallow and the orbital roofs may assume a nearly vertical position. The middle fossa may be abnormally deep and the auditory meati may assume a low position. The superior orbital fissure is short and narrow. The frontal sinuses are small. There may be signs of increased intracranial pressure as evidenced by digital markings over the vault and decalcification of the dorsum sella. Sear[13] has reported a case in which there was a Lückenschädel. The skull is usually thinned, but occasionally it may be thicker than normal. The thinning, if it does occur, is at the expense of the diploe. Sear has shown that the basal angle is altered in these patients. In scaphocephaly there is a platybasia with an increase in the basilar angle, and in oxycephaly there is a basilar kyphosis with a decrease in the basilar angle. Decrease in the size of the optic foramen has been reported in a few cases.

Careful study of the roentgenograms is especially important if surgical intervention is considered because the surgical procedure which is chosen may in large part depend upon which sutures are synostosed.

DIAGNOSIS

When craniostenosis is severe the diagnosis of this anomaly is a relatively simple matter. The typical cranial deformity, the associated deformities of the bones of the face and of the extremities, signs of increased intracranial pressure, evidence of cerebral damage, and the typical roentgenographic findings, all serve as unmistakable signposts to a correct diagnosis.

However, if treatment is to achieve maximum results, the diagnosis must be made prior to the time that irreparable damage has been done to the brain by the nonyielding skull. In the early stages of craniostenosis the diagnosis is much more difficult. Roentgenographic evidence of obliteration of one or more sutures must be present in order to make a diagnosis of craniostenosis. However, roentgenographic evidence of premature closure of suture lines is not in itself irrefutable proof of the presence of craniostenosis. This is true because of the difficulty at times of satisfactorily demonstrating the sutures roentgenographically in normal children, especially if the skull is thin so that the contrast between suture and bone is poor.

The shape of the skull itself is of great importance and measurement of its expansion over a period of time should be carefully plotted to see how closely it approaches the normal growth curve. The shape of the skull in young patients will not be as definitely abnormal as it will at a later date, and the great variability in the shape of normal skulls adds to the difficulty in making a correct diagnosis. Still, one is not justified in temporizing until the head

is unmistakably small or until it is extremely abnormal in shape before arriving at a correct diagnosis and instituting surgical treatment.

The typical deformities so frequently associated with craniostenosis, if present, may be of the utmost value in arriving at the diagnosis. Thus, if the typical facial deformities or deformities in the extremities are present, they establish the diagnosis even with minimal cranial vault deformity.

Careful family histories may reveal that similar deformities are present in other members of the family, and this, together with even minimal findings in a patient, is enough to make a diagnosis early in the course of the disease.

Visual difficulties and signs of increased intracranial pressure occur late in the course of the disease, and, if possible, surgical treatment should be instituted before these occur. By the time these symptoms are present, there has undoubtedly been damage to the brain and the optimum time for surgical intervention is past.

Mental development is retarded in these children, and this may be the primary indication for surgical therapy. However, it is often extremely difficult to differentiate craniostenosis from microcephaly, which is also characterized by decreased expansion of the skull and early synostosis of the cranial sutures. In many instances, excellent clinical judgment will be necessary to determine whether or not a true craniostenosis is present.

TREATMENT

In the latter part of the last century the first attempts were made at surgical intervention in cases of children with small heads. In 1890, Lannelongue[4] reported the case of a 4-year-old girl with microcephaly and idiocy, on whom he performed a linear craniectomy paralleling the sagittal suture, and reported improvement in mentality following the operation. In 1892, Lane[5] reported two cases in which cruciate types of linear craniectomies were performed. A strip of bone was removed parallel to the sagittal suture and another strip just posterior to the coronal suture. The first patient died fourteen hours postoperatively, and in the second case Lane reported there was some improvement in mentality following the operation. It is now evident on reading the case histories reported by these surgeons that the children operated upon had microcephaly rather than craniostenosis, but the authors did not recognize the difference between these two conditions. In 1894, Jacobi[6] was able to collect reports of thirty-three operations performed in America either for premature synostosis or microcephaly. Of this group there were fourteen postoperative deaths. He criticized severely those who were performing operations on microcephalics, although he admitted that operative procedures might be useful in cases of premature synostosis. Surgery for craniostenosis fell into disrepute, because most surgeons apparently did not recognize the difference between craniostenosis and microcephaly, and because there was such a high operative mortality. There are still many who feel that successful treatment of craniostenosis is impossible.

In 1908, Dorfmann[44] reported a case of a 4-year-old girl with oxycephaly and severe papilledema. This case was trephined by Eiselberg, and Dorfmann felt that the operation was successful in saving the patient's vision. Since that time Sharpe,[31] Bedell,[21] Watts,[45] Skipper,[28] and Bennett and co-workers[41] have all reported cases in which either unilateral or bilateral subtemporal decompressions have been done to relieve symptoms resulting from increased intracranial pressure. Bedell[21] had one patient who died immediately postoperatively, but other reports have all been favorable, and would indicate that the operation has merit. However, the total number of cases in whom this procedure has been done is small, and the patients have been followed for too short a time after surgery to arrive at any definite conclusions as to the results of subtemporal decompression in the treatment of this anomaly.

In 1913, Schloffer[37] first recommended resection of a portion of the roof of the orbit adjacent to the optic nerve to relieve the visual symptoms in these cases. He felt, as have other investigators, that the optic atrophy and papilledema so commonly seen in cases of craniostenosis was due to direct constriction of the optic nerve rather than to generalized increased intracranial pressure. Hildebrand,[46] in 1923, reported four cases in whom a modified form of the Schloffer operation was performed to relieve increasing visual impairment, and he reported that the results were satisfactory in all four cases. In 1924, Elschnig[47] performed this operation on three patients but he reported no follow-up studies on the patients. Schloffer's operation has not been used outside of Germany, and most investigators believe that the operation has no value because it is based on the false premise that the visual difficulties are due to direct optic nerve involvement rather than to increased intracranial pressure.

Bauer,[48] in 1932, reported on one case in which a circular type of craniectomy was performed, separating the vault from the remainder of the skull, thereby permitting an increase in intracranial capacity by elevation of the separated portion of the vault. The dura was not opened. Bauer claimed that there was no new bone formation six months after the operation, but the published reproductions of the roentgenograms on the patient seem to show that new bone was present at the site of the craniectomy. Although Bauer has been given credit for developing this operation, Sharpe[31] reports that Cushing, in 1911, performed the same operation but abandoned it because of the rapid regeneration of bone which prevented adequate expansion of the skull. Bennett and co-workers[41] in 1936 used this circular craniectomy in one case. Results of these operations are not known.

King,[49] in 1938, proposed a procedure for the treatment of craniostenosis which he calls the morcellation operation. Multiple grooves are cut through the skull, separating the cranial vault into a checkerboard pattern. King believed that this procedure would allow for a more symmetrical expansion of the brain than any of the previously suggested procedures. King[49-51] and Woodhall[52] have reported a total of seven patients on whom this morcellation operation was performed with satisfactory results.

Faber and Towne[42, 43] have again advocated the use of a linear craniectomy as used by Lane[5] and Lannelongue[4] during the last century. They have reported five patients on whom this operation was performed, and their results have been encouraging. They have been able to observe one of the patients for

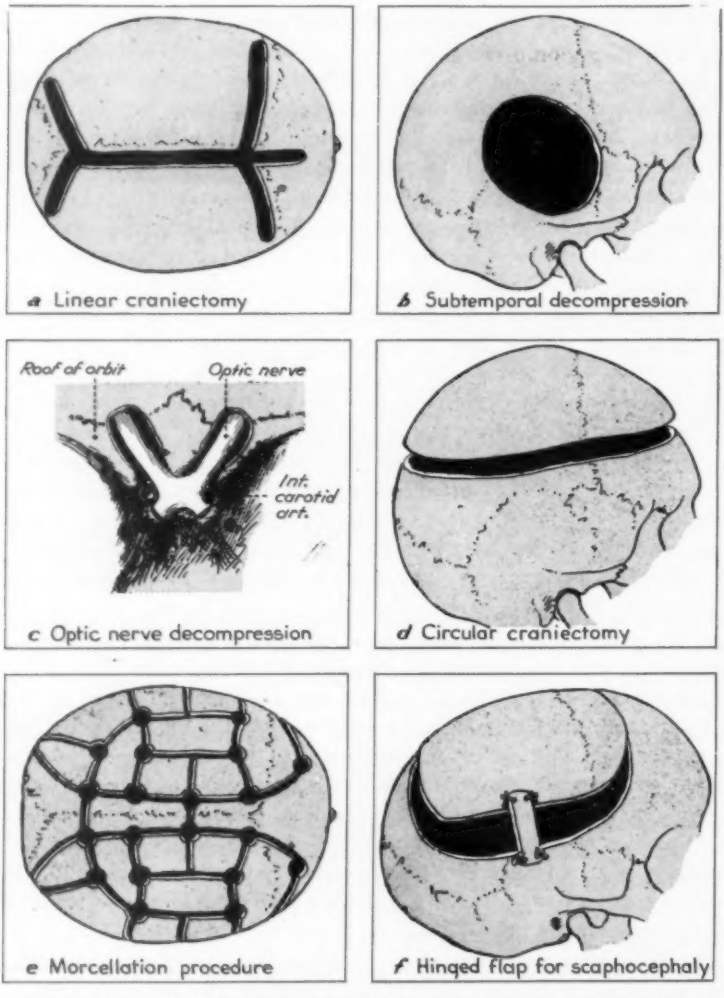

Fig. 3.—Operations which have been used in the treatment of craniostenosis.

a period of fourteen years following operation, and the result in this case has been excellent. This is the only reported case in which there has been a postoperative period of observation of sufficient length so that the eventual result after operation could be evaluated. Faber and Towne[42] were the first to point

out that early operation is imperative if these patients are to receive maximum relief of symptoms. This is true because the period of rapid brain growth occurs in the first few months of life, and if operation is delayed until after 6 or 8 months of age, the damage to the brain may be severe and irreparable, and operation may be of little benefit.

Dandy,[53] in 1943, reported a new operative technique for the treatment of craniostenosis. He turns a large frontoparietal horseshoe-shaped bone flap with its base hinged at the midline. The flap is then elevated from its bed and held in this elevated position like a trap door by a small piece of bone which is fastened to the inferior edge of the flap, and the squamous portion of the temporal bone. This operation would appear to be technically more difficult than others which have been proposed, and it would not seem to be any more effective in increasing the volume of the intracranial cavity.

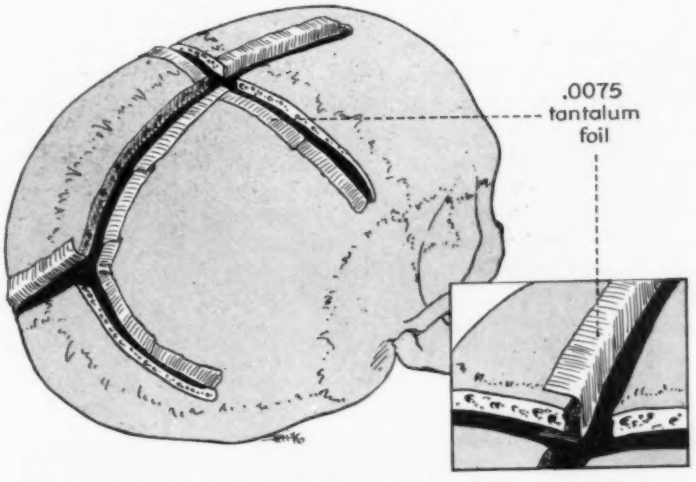

Fig. 4.—Method of using tantalum foil to prevent bridging of the craniectomy by new bone formation.

Even in recent years it has been stated that there are no therapeutic measures which are successful in relieving the symptoms resulting from craniostenosis, but this certainly has not been the experience of most surgeons who have operated on these patients. Although the results are not perfect, a certain measure of relief of symptoms has been obtained in most cases, and in at least one case[43] the final condition many years after operation was very satisfactory.

The large majority of cases of craniostenosis are not of severe degree, and in these cases no therapy is necessary. However, there are certain very definite indications for surgical intervention. Probably the most important indication for surgical intervention in cases of craniostenosis is mental retardation. This indication for surgical therapy has received too little emphasis in the literature. Mental retardation is one of the earliest symptoms, and in many cases of cranio-

stenosis is probably the only symptom throughout life. Every child with craniostenosis should be watched closely for mental retardation, and surgical therapy should be instituted at the first sign of such retardation. It cannot be emphasized too strongly that if the surgery is to be of maximum benefit in preventing further mental retardation it must be done at an early age. Faber and Towne[42, 43] have recommended that these patients be operated before the age of 6 months because if surgery is delayed longer than this, irreparable damage is sustained by the brain. Blindness is one of the most common symptoms in this disease, and surgery should be done at the first indication of failing vision. Günther[30] found that in seventy-four cases collected from the literature, sixty-seven patients had optic atrophy and forty-five were amaurotic. Brai[34] in reviewing the literature on oxycephaly, found that of a total of eighty-five patients, twenty-five had a bilateral total amaurosis, and in thirty additional ones there was a unilateral amaurosis. Occasionally surgery may be necessary for the relief of severe and persistent headaches which accompany the disease.

Many operative procedures, several of which have merit, have been recommended for the treatment of the disease (Fig. 3). Each individual case must be evaluated and the operative procedure which seems most applicable to it chosen. In infants, the linear type of craniectomy, as used many years ago by Lane and Lannelongue and as advocated by Faber and Towne in recent years, appears to be most useful. Because the bones of the skull in infants are thin and flexible, the linear type of craniectomy will allow for adequate expansion of the brain, and will allow the head to assume a normal shape. After linear craniectomy, especially in children, the bone tends to form bridges across the artificial suture lines and expansion is again arrested. This growth of bone across the craniectomy is probably one of the reasons for poor results following surgical intervention in these cases. Tantalum foil interposed between the bone edges should prevent this regeneration and allow continued expansion of the skull without additional operations. The method of using tantalum foil is illustrated in Fig. 4. It has now been used in two cases (Case 1 and Case 4).

The morcellation procedure proposed by King is useful in older children in whom the skull is so thick and rigid that a linear craniectomy alone will not allow for adequate expansion of the brain and resumption of a normal shape by the skull. Subtemporal decompression is useful in adults with visual difficulties and headaches, and may be preferable to the morcellation operation because of its simplicity. The operations of Bauer[47] and Dandy[50] are not recommended because they seem to be technically more difficult, and they are probably no more effective in increasing the intracranial volume than are the other operations.

Decompression of the optic canal as proposed by Schloffer[37] has not been widely accepted, but it is possible that in certain cases visual impairment is due to direct pressure on the optic nerves, and if so, this operation should give relief. At least it should be considered if loss of vision is progressive after increased intracranial pressure is eliminated by one of the previously described operations.

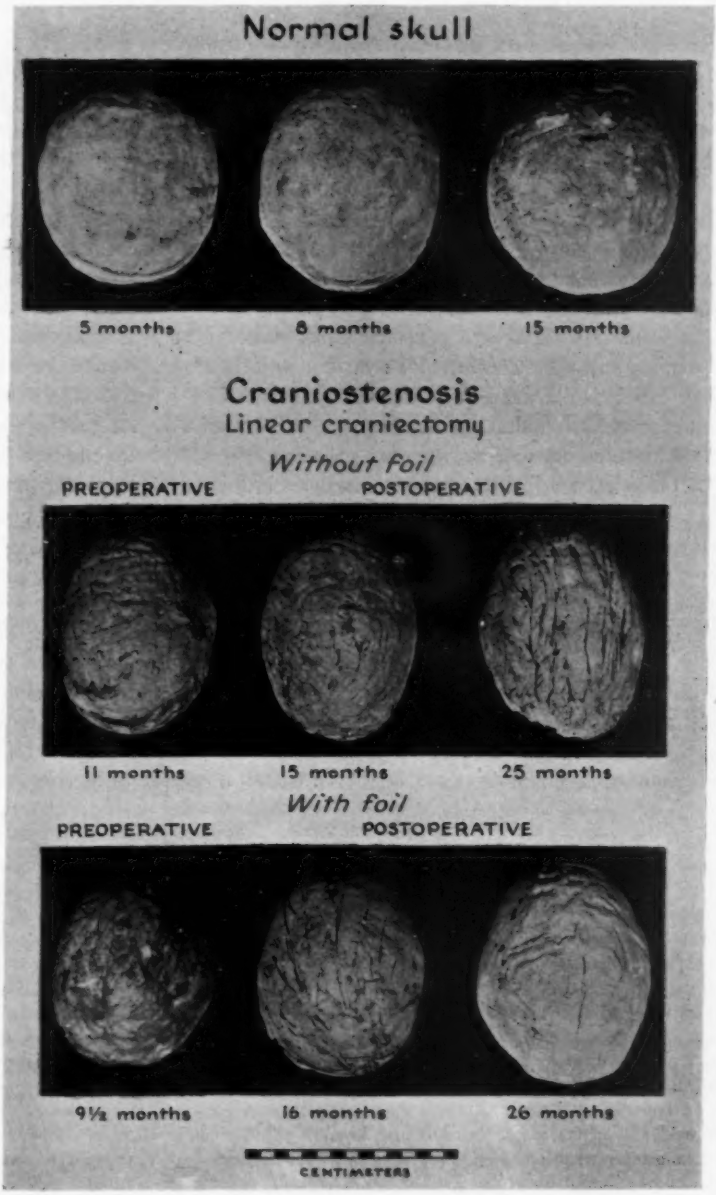

Fig. 5.—*A*, Cast of the cranial vault at 5, 8, and 15 months of age in a normal child.

B, Similar casts in Case 1. This patient had a linear craniectomy without the use of tantalum foil.

C, Case 4, in which tantalum foil was used. There is greater enlargement of the skull than in Case 1.

PROGNOSIS

There are few reports in the literature concerning the prognosis in this disease. Since the large majority of the cases reported have been in children and young adults, one might suspect that this indicates that the life expectancy is less than that of normal individuals, but there can be no doubt that premature synostosis is at times associated with longevity. Fletcher[25] said that although cases are rarely seen among people over 50 years of age, there is no direct evidence that the disease shortens life. The prognosis for life probably depends in large measure upon the severity of the disease process. There seems little doubt that there will be impairment of intelligence in a large number of these patients. Again, this depends largely on the severity of the process. Certainly, in every case of severe premature synostosis there is a danger of optic atrophy and blindness. This usually occurs in childhood, but it may occur later. Elsehnig[46] reported a case of a 50-year-old man with visual impairment of increasing severity. Thus, the danger of loss of vision is not past when the brain has attained its full growth but it is most prevalent during the period of rapid brain growth, which in turn produces increased intracranial pressure.

To what extent the prognosis can be altered by surgical therapy is not definitely known. This is true because of the small number of cases that have been operated upon and followed for a sufficient period of time to be accurately evaluated. Long term follow-up study has been reported in only a single case.[42] This child was operated upon in 1927 and followed until 1941, when he was perfectly normal in every respect. This case makes one hopeful as to the results which may be obtained by surgical intervention, but certainly we are not yet justified in drawing any final conclusions as to its efficacy. The most one may say is that as a method of therapy it appears to be rational, and that in isolated instances the results as far as they are known appear to be encouraging.

CASE REPORTS

CASE 1.—An 11-month-old male infant was admitted to the hospital with a history of periods of "bobbing" of the head for three months. Examination revealed the skull to be scaphocephalic and the fontanelles were closed. The head circumference was 48 cm. There was moderate mental retardation. Roentgenographic examination of the skull revealed synostosis of the sagittal suture, decalcification of the dorsum sellae, and an increase in the basalar angle. Strips of bone 1 cm. in width were removed paralleling the sagittal and coronal sutures together with the overlying periosteum. Postoperatively the bobbing of the head disappeared but seven months after operation there was roentgenographic evidence of regeneration of bone across the craniectomy defect. Twenty months after operation, a Stanford-Binet (Form M) test showed an I.Q. of 80 and roentgenograms of the skull revealed an increase in digital markings suggesting increased intracranial pressure. Because of this evidence of increased pressure and because of the regeneration of bone, a second linear craniectomy was done twenty-six months after the first, and tantalum foil was placed over the edge of the bone. The patient has been observed for three months following the second operation and there have been no changes in his status.

CASE 2.—A 3½-year-old boy was admitted to the hospital with a history of prominent eyes, an abnormally shaped skull, and a watery nasal discharge since birth. He had progres-

sive loss of vision for a few months. The patient's mother and a maternal uncle had abnormally shaped heads. Examination revealed an oxycephalic skull and a head circumference of 44 cm. There was bilateral exophthalmos, bilateral optic atrophy, a beak-shaped nose, hypertelorism, divergent strabismus, a prognathous jaw, a highly arched palate, and a narrow maxilla with crowding of the teeth. Psychometric testing revealed the child to be in the lowest range of normal intelligence. Roentgenograms of the skull revealed oxycephaly and synostosis of all sutures of the cranial vault, but the nasofrontal and spheno-occipital sutures were open. The posterior fossa was deep, the orbits shallow, and the orbital roofs were more nearly vertical than normal.

A linear craniectomy was done paralleling the sagittal, coronal, and lambdoid sutures. Four months after operation he seemed more alert and active than he had preoperatively. The head circumference increased 5½ cm. in these four months. Psychometric examination fourteen months after operation revealed a slight improvement in intelligence over his preoperative level. His head circumference was 50 cm.

CASE 3.—This 28-year-old female, the mother of Case 2, had severe scaphocephaly, bilateral exophthalmos, a beak shaped nose, prognathous jaw, and hypertelorism. Roentgenograms revealed marked scaphocephaly with obliteration of all sutures of the cranial vault.

CASE 4.—An 8-month-old male infant was admitted to the hospital because the attending pediatrician had noted closure of the fontanelles at 8 weeks of age, development of scaphocephaly, and lack of adequate mental development for two months. Examination revealed scaphocephaly, closed fontanelles, and a head circumference of 44 cm. Roentgenograms of the skull showed obliteration of the sagittal and coronal sutures. A linear craniectomy was performed paralleling the sagittal and coronal sutures and tantalum foil was used to cover the bone edge. Six months after operation the head circumference was 48 cm. and the mental development seemed normal. One year after operation psychometric testing revealed the patient to have an I.Q. of 100 and he seemed in every way to be a normal child.

CASE 5.—A 29-year-old woman was admitted to the hospital with complaints of frontal headaches for many years, and an abnormally shaped head, bilateral exophthalomos, and poor vision since early childhood. Examination revealed oxycephaly, bilateral exophthalmos, bilateral optic atrophy, and a high arched palate. Roentgenograms of the skull revealed a severe degree of oxycephaly with increased digital markings. Bilateral myoplastic subtemporal decompressions were performed and following these procedures her headaches were much less frequent and less severe.

CONCLUSIONS

1. The condition which gives most difficulty in the differential diagnosis of craniostenosis is microcephaly, but in the large majority of cases it should be possible to distinguish between these two conditions at an early age.

2. While the results following surgical therapy for craniostenosis have not been completely satisfactory in the past, it seems likely that earlier recognition of cases together with technical improvements in operative procedures can bring better results in the future.

3. It appears that an important indication for surgical intervention in craniostenosis and one which has received little emphasis in the past, is mental retardation. It is, of course, impossible to repair brain damage which has already occurred, but further brain damage may be prevented by craniectomy. If continued mental retardation is to be prevented, these cases must be operated early.

4. One reason for the unsatisfactory results of operations for craniostenosis is that bone quickly grows across the craniectomy defect. A method of using tantalum foil to prevent such bone regeneration is presented.

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PHTHALYLSULFATHIAZOLE IN THE TREATMENT OF DIARRHEA IN CHILDREN

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THE treatment of acute microbic diarrhea during infancy and childhood has become more satisfactory since the sulfonamides have been used as adjuvants to a limited bland diet and adequate parenteral and oral fluids. The periods of acute illness and of convalesence have been shortened, mortality rate lowered, and "days in the hospital" reduced. Stool cultures have become negative sooner, resulting in earlier release from isolation technique and quarantine. The early in vivo disinfection of the stool results in a saving of hospital quarantine days, and it eliminated carriers, recurrences, and secondary contact cases.

Although chemically similar, two types of sulfonamides with different physical and pharmacodynamic characteristics have been synthesized and used successfully in the treatment of children with diarrhea. One is very soluble, is absorbed quickly, and is circulated in the blood in a high concentration. The other is only slightly soluble, is absorbed poorly, and produces a low blood but high intestinal concentration. The successful response to the drugs with paradoxical physical characteristics has stimulated the synthesis and clinical investigation of new compounds of both types.

In 1941, Poth and Knotts[4] reported excellent results with succinylsulfathiazole as an intestinal antiseptic, and in 1943 Poth and Ross[2] introduced phthalylsulfathiazole. Their investigation showed the latter sulfonamide to be four times as effective as succinylsulfathiazole as a gastrointestinal bacteriostatic. Their tests were made on dogs. Coliform colonies obtained from the feces of the experimental animals were used as indicators. They demonstrated that the drug was sparingly absorbed and that it had extremely low toxicity. The low toxicity was further demonstrated by Mattis and associates.[1] They gave doses of 10 Gm. per kilogram to white mice and 5 Gm. per kilogram per day for thirty days to monkeys without toxic effect.

Based on the favorable reports, a therapeutic evaluation of phthalylsulfathiazole as an intestinal antiseptic was undertaken. During the summer and fall of 1943, 121 patients entered the Children's Division of Cook County Hospital with a history of abnormally frequent and liquid stools during the preceeding few hours. Following admission, a diagnosis of diarrhea was established in ninety-eight of these (Group A).

From Children's Division of Cook County Hospital and the Hektoen Institute for Medical Research of Cook County Hospital.
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*Deceased.

In the remaining twenty-three, the number of stools passed within the first twenty-four hours after admission was less than three, and these children are grouped separately (Group B). Fifty-seven other children admitted to the hospital with complaints not associated with the gastrointestinal tract (Group C), had stool examinations for comparison with the other groups.

Of Group A, twenty-five were treated with phthalylsulfathiazole, twenty-nine with sulfathiazole, ten with kaopectate, and two, diagnosed as typhoid fever, with sulfaguanidine, respectively. The thirty-two others of this group were treated with various combinations of these drugs. Forty-six of the patients in Group A were under, and fifty-two were over 12 months of age. Three deaths occurred, all in children under 12 months of age. (Table I). Of Group B, six were treated with phthalylsulfathiazole, thirteen with sulfathiazole, one with kaopectate, and three with combinations of these drugs. (Table II.)

Bacteriologic cultures of 291 stools obtained from the ninety-eight children with diarrhea (Group A) were studied. Two typhoid fever patients were included in this group although neither of these had diarrhea. Forty-four stools of twenty-three other patients (Group B) with an admission complaint of frequent evacuations were examined. These patients were grouped separately and not included in the diarrheal series because they did not meet the requirements of our definition of diarrhea, that is three or more stools during the first twenty-four hours after admission. The stools of the fifty-seven children in group C with symptoms unrelated to the gastrointestinal tract, were examined to determine the incidence of recognized diarrhea producing organisms in nondiarrheal stools in the hospital population.

From the stools of eighteen (20 per cent) of the children in Group A, *Shigella dysenteriae* or *paradysenteriae* was cultured in twenty-six instances, *Eberthella typhosa* in two (2 per cent) instances, and *Salmonella paratyphi* (*Salmonella manhattan*) in one instance (1 per cent). *S. dysenteriae* was cultured in seven instances in six (25 per cent) of the patients in Group B. No dysentery pathogens were recovered from the stools of the fifty-seven patients in Group C. *Proteus morganii* was cultured from the stools of seven (7 per cent) of the ninety-eight children in the diarrheal group, from four (16 per cent) of the twenty-three in Group B and from three (5 per cent) of those in Group C.

Because of the difference in prognosis, the children with diarrhea (Group A) have been divided into two subgroups. The first includes those under, and the second those over, 12 months of age.

The incidence of severity of the disease and the response to specific drugs is shown, together with the bacteriologic findings in the feces of each of these subgroups. (Tables III and IV.)

The sulfonamides studied were given in divided doses of at least one grain per pound of body weight in twenty-four hours. The results of 126 determinations for the sulfonamide content of the blood are shown in Table V. There were thirty-five sulfonamide blood level determinations on patients receiving phthalylsulfathiazole; twenty-nine of these were less than one milligram in 100

TABLE I. THERAPY, AGE DISTRIBUTION, AND RESULTS

TYPE OF MEDICATION	AGE DISTRIBUTION: UNDER 12 MONTHS NO. CASES	UNDER 12 MONTHS AV. DAYS OF DIARRHEA AFTER MEDICATION	OVER 12 MONTHS NO. CASES	OVER 12 MONTHS AV. DAYS OF DIARRHEA AFTER MEDICATION	RESULTS: TOTALS NO. CASES	TOTALS AV. DAYS OF DIARRHEA AFTER MEDICATION	RECOVERED	DEATHS
Phthalylsulfathiazole	8	5.9	17	2.5	25	3.6	25	0
Phthalylsulfathiazole and sulfathiazole	3	4.6	1	1.9	4	3.8	3	1
Phthalylsulfathiazole and kaopectate	1	16.0	7	4.6	8	6.0	8	0
Phthalylsulfathiazole and kaopectate sulfathiazole	3	11.3	0	0	3	11.3	1	2
Phthalylsulfathiazole and kaopectate sulfamerazine	0	0	1	5.0	1	5.0	1	0
Total	15	7.7	26	3.1	41	4.6	38	3
Sulfathiazole	14	3.9	15	1.7	29	2.7	29	0
Sulfathiazole and kaopectate	8	6.4	1	1.0	9	5.8	9	0
Sulfathiazole and sulfamerazine	1	6.0	0	0	1	6.0	1	0
Sulfathiazole and kaopectate and nipectin	2	7.5	0	0	2	7.5	2	0
Sulfathiazole and nipectin	1	4.0	0	0	1	4.0	1	0
Total	26	5.0	16	1.6	42	3.7	42	0
Kaopectate	2	8.0	8	4.0	10	4.8	10	0
Kaopectate and nipectin	2	6.0	0	0	2	6.0	2	0
Kaopectate and Sulfamerazine	1	4.0	0	0	1	4.0	1	0
Total	5	6.4	8	4.0	13	4.9	13	0
Sulfaguanadine	0	0	2	0	2	0	2	0
Totals	46	—	52	—	98	—	95	3

TABLE II. THERAPY AND AGE DISTRIBUTION OF THE CASES IN GROUP B

TYPE OF MEDICATION	AGE DISTRIBUTION: UNDER 12 MONTHS NON-SPECIFIC	UNDER 12 MONTHS SPECIFIC	UNDER 12 MONTHS TOTALS	OVER 12 MONTHS NON-SPECIFIC	OVER 12 MONTHS SPECIFIC	OVER 12 MONTHS TOTALS	TOTALS
Phthalylsulfathiazole	1	0	1	3	2	5	6
Phthalylsulfathiazole and sulfathiazole	0	0	0	1	0	1	1
Phthalylsulfathiazole and kaopectate	0	0	0	1	0	1	1
Total	1	0	1	5	2	7	8
Sulfathiazole	5	0	5	4	4	8	13
Sulfathiazole and kaopectate	0	0	0	1	0	1	1
Total	5	0	5	5	4	9	14
Kaopectate	0	0	0	1	0	1	1
Total	0	0	0	1	0	1	1
Totals	6	0	6	11	6	17	23

TABLE III. CORRELATION OF SEVERITY OF DIARRHEA, BACTERIOLOGY, AND RESPONSE TO MEDICATION IN CHILDREN UNDER TWELVE MONTHS OF AGE

MEDICATION		BACTERIOLOGY				RESULTS			
		NONSPECIFIC		DYSENTERY					
TYPE	SEVERITY	NO. CASES	AVERAGE DAYS DIARRHEA AFTER MEDICATION	NO. CASES	AVERAGE DAYS DIARRHEA AFTER MEDICATION	TOTAL NO. CASES	AVERAGE DAYS DIARRHEA AFTER MEDICATION	RECOVERED	DEATHS
Phthalylsulfathiazole									
	Severe	1	6.0	0	0	1	6.0	1	0
	Moderate	5	6.4	0	0	5	6.4	5	0
	Mild	2	4.5	0	0	2	4.5	2	0
Total		8	5.9	0	0	8	5.9	8	0
Kaopectate									
	Severe	0	0	0	0	0	0	0	0
	Moderate	1	12.0	0	0	1	12.0	1	0
	Mild	1	4.0	0	0	1	4.0	1	0
Total		2	7.0	0	0	2	7.0	2	0
Sulfathiazole									
	Severe	1	10.0	0	0	1	10.0	1	0
	Moderate	6	3.6	0	0	6	3.6	6	0
	Mild	7	3.1	0	0	7	3.1	7	0
Total		14	3.8	0	0	14	3.8	14	0
Combinations									
		(+2	15.5	0	0	+2	15.5	0	2)
	Severe	2	7.5	0	0	2	7.5	2	0
		(++1	2.0	0	0	++1	2.0	0	1)
	Moderate	11	7.4	0	0	11	7.4	11	0
	Mild	5	4.4	1	5.0	6	4.5	6	0
		(+,++3	11.0	0	0	+,++3	11.0	0	3)
Total		18	6.6	1	5.0	19	6.4	19	0

+, two deaths with persistence of diarrhea for twenty and eleven days, respectively.
++, one death with persistence of diarrhea for two days.

c.c. of blood (usually reported as "none" or a "trace"). The remaining six levels ranged from 1 to 4 mg. Of the thirty-two sulfonamide determinations on children receiving sulfathiazole, seven were less than one milligram, four between one and 2, eight between 2 and 3, five between 3 and 4 and six between 4 and 5 mg. per cent. The remaining two blood levels were over 5 mg. Fifty-nine determinations were made on the blood of children receiving combinations of sulfonamides. They ranged from 0 to 7 and 8 mg. per cent. No child manifested any symptoms suggestive of a toxic reaction to any of the sulfonamides.

Diarrhea was classified from the number of stools during the first twenty-four hours after admission as mild if more than three but less than five, moderate if five to seven, severe if there were seven or more stools in twenty-four hours. When a patient of the diarrheal series passed fewer than three stools in twenty-four hours, he was classified as "recovered." In all instances, the first stool after admission was cultured, and drug therapy instituted immediately thereafter without awaiting the bacteriologic results. The efficacy of the treatment was estimated from the number of days diarrhea persisted after the institution of the specific drug.

The twenty-five diarrheal patients receiving phthalylsulfathiazole alone (Table I) recovered after an average of 3.6 days of medication. The sixteen re-

TABLE IV. CORRELATION OF SEVERITY OF DIARRHEA, BACTERIOLOGY, AND RESPONSE TO MEDICATION IN CHILDREN OVER TWELVE MONTHS OF AGE

MEDICATION		BACTERIOLOGY				RESULTS			
		NONSPECIFIC		DYSENTERY		TOTALS			
TYPE	SEVERITY	NO. CASES	AV. DAYS DIARRHEA AFTER MEDICATION	NO. CASES	AV. DAYS DIARRHEA AFTER MEDICATION	NO. CASES	AV. DAYS DIARRHEA AFTER MEDICATION	RECOVERED	DEATHS
Phthalylsulfathiazole	Severe	2	2.5	4	3.5	6	3.2	6	0
	Moderate	2	2.5	0	0	2	2.5	2	0
	Mild	5	1.4	4	2.7	9	2.0	9	0
Total		9	1.9	8	3.1	17	2.5	17	0
Kaopectate									
	Severe	0	0	0	0	0	0	0	0
	Moderate	2	4.0	1	9.0	3	5.7	3	0
	Mild	3	3.3	2	2.5	5	3.0	5	0
Total		5	3.5	3	4.6	8	4.0	8	0
Sulfathiazole									
	Severe	2	2.0	1	2.0	3	2.0	3	0
	Moderate	3	2.0	0	0	3	2.0	3	0
	Mild	6	1.5	3	1.3	9	1.4	9	0
Total		11	1.8	4	1.5	15	1.6	15	0
Combinations									
	Severe	0	0	0	0	0	0	0	0
	Moderate	3	6.3	1	10.0	4	7.2	4	0
	Mild	5	1.8	1	1.0	6	1.7	6	0
		8	3.5	2	5.5	10	3.9	10	0

TABLE V. SULFONAMIDE BLOOD LEVELS OBTAINED WITH SULFATHIAZOLE AND COMBINATIONS OF THESE TWO DRUGS

THERAPY	BLOOD LEVELS IN MG. %								TOTALS
	0-1%	1-2%	2-3%	3-4%	4-5%	5-6%	6-7%	7-8%	
No. determinations for									
Phthalylsulfathiazole	29	2	1	3	0	0	0	0	35
Sulfathiazole	7	4	8	5	6	2	0	0	32
Combination of sulfonamides	36	7	3	7	3	1	1	1	59
Totals	72	13	12	15	9	3	1	1	126

ceiving this drug in combination with sulfathiazole, kaopectate, and/or sulfamerazine required an average of 6.7 days for cure. The twenty-nine patients receiving sulfathiazole alone recovered in 2.7 days. The use of sulfathiazole with kaopectate, sulfamerazine, and/or nipectin in thirteen cases was followed by recovery after an average of 6.7 days. In ten patients given kaopectate only, recovery followed in an average of 4.8 days. Two children given a combination of kaopectate and nipectin recovered in six days. Kaopectate and sulfamerazine used together in one case was followed by the reduction of the number of stools to normal in 4 days.

There were forty-six infants in the subgroup of diarrheal cases under 12 months of age (Table III). Eight of these receiving phthalylsulfathiazole alone recovered in an average of 5.8 days. The fourteen treated with sulfathiazole alone recovered in 3.8 days. Kaopectate alone given to two cases was followed by reduction of the number of stools to normal in 7 days. In

twenty-two cases, the use of combinations of the three medicaments was followed by death in three instances and by recovery in nineteen in an average of 6.4 days.

The three children that died received phthalylsulfathiazole and sulfathiazole and two received kaopectate in addition. The postmortem examination of these three infants revealed marked cachexia and malnutrition. Nonspecific enteritis was found in two; in one it was complicated by aspiration bronchopneumonia, and in another by an old peritonitis with firm adhesions to the gall bladder. Associated with the peritonitis was mesenteric glandular hyperplasia.

The treatment of the three children who died included in all instances a period of marked restriction of oral intake of food, intravenous plasma, blood, and saline or Hartman's solution infusions. Phthalylsulfathiazole and sulfathiazole were given to the three infants in doses of one grain to 3 grains per pound body weight in twenty-four hours for the entire duration of their hospital stay, which ranged from two to twenty days. Kaopectate was given to two, as was parenteral Vitamin B. In one instance, sulfathiazole was given as the sodium salt, intravenously. There were eight determinations for sulfonamide content in the blood; all were reported as "trace" or "none."

In the subgroup of diarrheal patients over 12 months of age, there were fifty children (Table IV). (The two cases of typhoid fever are not included.) Of these, seventeen were treated with phthalylsulfathiazole alone; they recovered after an average of 2.5 days. The fifteen patients treated with sulfathiazole recovered after an average of 1.6 days. The eight receiving kaopectate required 4 days before they could be considered "cured." Ten patients receiving a combination of medicaments had a persistence of diarrhea for 3.9 days. The two typhoid fever patients were treated with sulfaguanidine although they had no diarrhea.

From the stools of nineteen of the ninety-eight patients with diarrhea (Group A), organisms commonly accepted as active etiologic factors in dysentery were obtained one or more times. Repeated examinations of stools in the other seventy-seven patients were negative. Only one positive culture occurred in the subgroup under 12 months of age; the other forty-five infants had negative stool cultures. Eighteen positive cultures were obtained from patients over 12 months of age; the stools of the remaining thirty-four were negative. Of the older children given phthalylsulfathiazole alone (Group A), nine were nonspecific and eight with specific diarrheas recovered in 1.9 and 3.1 days respectively. Eleven of the older children (Group A) with nonspecific and four with specific diarrhea, given sulfathiazole alone, recovered in 1.8 and 1.5 days, respectively. The use of kaopectate was followed by a reduction of the number of stools to normal in 3.6 days in five nonspecific and 4.6 days in three specific cases of diarrhea. The combination of the above drugs was followed by recovery in 3.5 days for the two specific cases of diarrhea. It is to be noted that there were no deaths in the subgroup of children over 12 months of age.

Twenty-three children (Group B) admitted because of a complaint of diarrhea were grouped separately because they did not conform to our definition of diarrhea (Table II). Six of these were under and seventeen over 12 months of age. Bacteriologic examination of forty-four stools from these patients resulted in the identification of *S. dysenteriae* in the feces of six patients (13 per cent), all over 12 months of age. This group of children was treated with the same medicament as the diarrheal group, but because of the absence of diarrhea, no statistical inferences as to their efficacy is drawn. No toxic effects were noted.

RESULTS

It will be seen from Table I that the response to all of the drugs apparently was more favorable in the group over 12 months of age than in those under, and that the response to sulfathiazole and its combinations apparently was more favorable in both age groups than was the response to phthalylsulfathiazole and its combinations and kaopectate and its combinations.

Table III is an analysis of the incidence of specific and nonspecific diarrheas in the group under 12 months of age. Three deaths occurred in this group in infants from whose feces specific organisms were *not* recovered. There was but one instance in which specific organisms causing diarrhea were recovered from the feces of the infants under 12 months of age. The response to the various drugs investigated showed a trend in favor of sulfathiazole and a superiority of phthalylsulfathiazole over kaopectate.

From Table IV, which is the analysis of the diarrheal group over 12 months of age, it would seem that there is a trend in favor of sulfathiazole. The recoveries on this drug occured in 1.6 days as compared with 2.5 on phthalylsulfathiazole and 4 on kaopectate. Sulfathiazole seems to have been more effective both in the specific and nonspecific diarrheas in this age group when compared with phthalylsulfathiazole or kaopectate. Phthalylsulfathiazole seemed more effective in the specific than in the nonspecific diarrheas.

In Table V is shown the results of 126 determinations of sulfonamide blood content. Very little phthalylsulfathiazole was absorbed in comparison with the absorption of sulfathiazole. Since there were no toxic symptoms in any of the cases, this has only academic significance.

A statistical analysis of the results following the use of phthalylsulfathiazole, sulfathiazole, and kaopectate, and their combinations in the treatment of diarrhea in the two groups of children, one under and the other over 12 months of age, reveals the following:

In an over-all statistical analysis, including all children in Group A, *no significant difference** was noted in the effects of any of the three drugs, phthalylsulfathiazole, sulfathiazole, and kaopectate.

A specific comparison was made of phthalylsulfathiazole alone and in combination with sulfathiazole and with kaopectate, and sulfathiazole alone was compared with its combinations with other drugs. A significant difference

*A difference was considered significant if it reached "the 5 per cent level of significance." This means that the chances are 1 in 20 that a difference as large as this could be obtained through errors of random sampling.

was found to exist in the results following the administration of the single drug when compared to its use in combinations. The multiple drugs did not produce as favorable results as followed the use of a single drug.*

In all the statistical analyses made, a significant difference was found to exist in the response to treatment of the two age groups (one under and the other over 12 months of age). The drugs, whether administered singly or in combination, were more effective on the older age group.

SUMMARY

1. There was no statistically significant difference in the results obtained following the administration of phthalylsulfathiazole in comparison with the results following the use of sulfathiazole in the treatment of diarrheas in the children at Cook County Hospital during 1943.

2. Combinations of phthalylsulfathiazole, or of sulfathiazole, with other drugs appeared to be less effective than the use of individual drugs.

3. Both phthalylsulfathiazole and sulfathiazole were more effective in the treatment of diarrheas in the children over 12 month of age than in those under that age

4. Although statistically not evident, sulfathiazole appeared to shorten the course of diarrhea, whether due to specific or nonspecific organisms, more than phthalylsulfathiazole in all age groups.

5. The trend of response in children with diarrheas due to specific organisms was more favorable following the administration of sulfathiazole than following phthalylsulfathiazole.

6. Sulfathiazole appeared to be more effective in the treatment of diarrheas due to specific organisms than it was in the treatment of the nonspecific cases. The difference, however, is not statistically significant.

7. No toxic symptoms were observed as a result of the use of any of these drugs.

8. The post-mortem findings of the three infants that expired showed no evidence of any ill effect from drug therapy.

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*This is statistically true, but patients receiving multiple drugs were not random samples. They were given more than one drug because of failure to respond to the initial medication.

PERTUSSIS-PARAPERTUSSIS VACCINE

ALWIN C. RAMBAR, M.D., AND KATHERINE HOWELL, M.D., CHICAGO, ILL., AND EDWARD J. DENENHOLZ, M.D., MODESTO, CALIF.

SECOND attacks of whooping cough, though uncommon, occur with sufficient frequency to arouse the suspicion that the clinical picture of this disease may be produced by two closely allied infections. This observation has had confirmation by both bacteriologic and immunologic studies. In 1937, Eldering and Kendrick[1] and Bradford and Slavin[2] independently isolated a small, gram-negative coccobacillus from patients clinically suspected of having whooping cough. These writers observed that the growth of this organism in forty-eight hours on Bordet-Gengou medium was more luxuriant than that of *Hemophilus pertussis*. The colonies were similar to those of *H. pertussis* in that they were moist, domelike with an entire edge, and possessed a pearllike luster; however, instead of the slight hazy hemolysis and slight browning characteristic of colonies of *H. pertussis*, there was produced a pronounced, distinct browning of the medium. On microscopic examination, the organism was morphologically indistinguishable from *H. pertussis*, being an ovoid, nonmotile, nonspore-forming, gram-negative rod. Subcultures from the colonies on Bordet's medium grew on plain agar and in broth, thereby precluding the classification of the organism in the hemophilus group of bacteria. This atypical coccobacillus, which was biochemically more active than *H. pertussis*, was named *B. parapertussis* by Eldering and Kendrick.[3]

Immunologic studies indicated that the organism possesses common and antigenic fractions with both *H. pertussis* and *Brucella bronchiseptica*, but is identical with neither.[4] According to Flosdorf,[5] *H. Pertussis* and *B. parapertussis* have a major specific antigen and a minor common one, the latter being responsible for the cross-agglutination between the two organisms. *B. parapertussis* produces pulmonary lesions in mice that resemble those of experimental murine pertussis.[6] It has also been shown that specific humoral antibodies develop during the course of infection with *B. parapertussis*, and that an attack of either pertussis or parapertussis confers no immunity against the other disease. Similarly, active immunization against pertussis does not protect against parapertussis.

In 1941, because of the clinical implications of some of the above studies, particularly the possibility that some of the failures after immunization with pertussis vaccine was due to infection with *B. parapertussis*, we had a vaccine prepared which contained equal parts of a concentrated solution of *H. pertussis* and *B. parapertussis*, so that each cubic centimeter contained a total of 20 billion

From the Sarah Morris Hospital for Children, and the Department of Bacteriology, Michael Reese Hospital, Chicago.

Funds and vaccine for this work were supplied by the Upjohn Company, Kalamazoo, Michigan.

killed bacteria. Active immunization against whooping cough is routinely performed in the Premature Infant Clinic of Michael Reese Hospital. We have previously reported the results of our studies with pertussis vaccination with special reference to optimum dosage (single strength, double strength) type of vaccine (plain, alum precipitated), time interval between doses, response of different age groups, and effect of stimulating doses.[7, 8] In both the previous and the present study, the opsonocytophagic test was utilized to measure antibody response after vaccination period. The technique and significance of the opsonocytophagic test in pertussis has been carefully described by Kendrick.[9, 10] A comparison of the response of children to a standard *H. pertussis* Phase I, vaccine, containing 20 billion killed bacteria per cubic centimeter and to the combined *H. pertussis* Phase I and *B. parapertussis* was made. It was not considered advisable to vaccinate with *B. parapertussis* alone, in view of the major necessity of protecting against whooping cough in infancy and childhood.

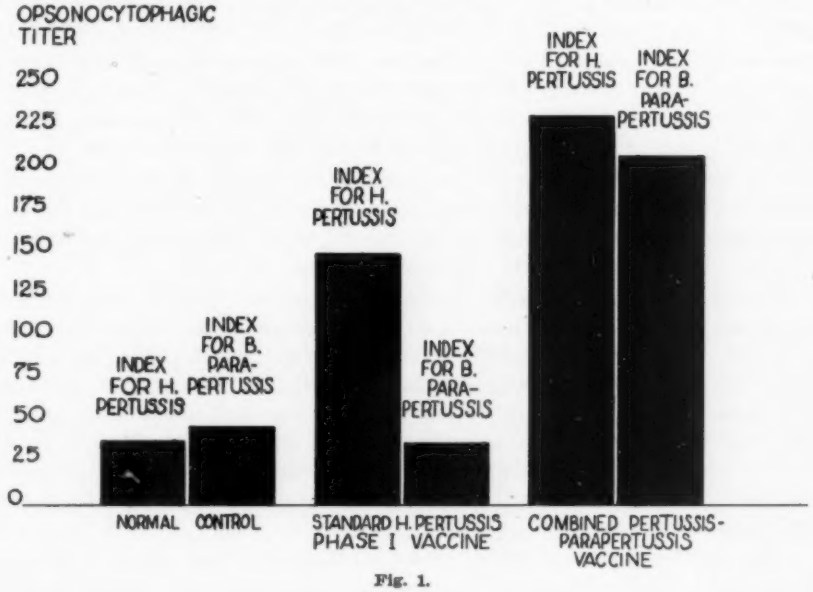

Fig. 1.

In order to establish the presence or absence of specific humoral antibodies prior to vaccination, a preliminary study was made. This consisted of determining the opsonocytophagic indices of twenty-five infants who were to receive the mixed vaccine and of twenty-five infants who were to be given *H. pertussis* vaccine alone. Results in these groups were identical, revealing an opsonocytophagic index for *H. pertussis* of 42 and for *B. parapertussis* of 48. These findings are well within the weak range that is usually encountered in nonimmune serum.[9, 10] These findings differ sharply from those of Miller and co-workers,[11] who reported that the agglutinins for *B. parapertussis* are widespread in children in California

and from those of Flosdorf and co-workers,[5] who reported similar findings in Philadelphia. It is possible that the low index for *B. parapertussis* in our patients can be attributed to the fact that our patient material was comprised only of young infants.

The patients for active immunization were divided into two equal groups on an alternate case basis. Thus each alternate patient received mixed vaccine (containing *H. pertussis* and *B. parapertussis*) and the other patients received plain vaccine (*H. pertussis* alone). Vaccination was started at six months in both of the groups studied. These infants represented a cross section of those seen in our clinic and were equally divided as to sex, with a preponderance of white over Negro. Only healthy infants were used in this survey. Inoculations were given at one-month intervals, one cubic centimeter the first injection, and 2 cubic centimeters each at the following injections, so that each infant received either a total of 100 billion killed *H. pertussis* Phase I bacteria in the standard vaccine, or 50 billion killed *H. pertussis* and 50 billion killed *B. parapertussis* bacteria in the mixed vaccine. Opsonocytophagic tests were made 6 months, 12 months, and 18 months after vaccination. The average index obtained after vaccination with *H. pertussis* alone was 149.7 for *H. pertussis*, while no appreciable change occurred in the *B. parapertussis* index, the average being 41, approximately that of normal serum obtained from nonvaccinated controls.

The average index obtained after vaccination with the mixed vaccine (*H. pertussis* Phase I and *B. parapertussis*), was 232.8 for *H. pertussis* and 208 for *B. parapertussis*. Both of these indices are well within the group of strong reactions, indicating a high state of immunity.

The fact that a higher index for each organism was obtained after using a mixed vaccine than after the use of the standard *H. pertussis* vaccine alone suggests that there may be synergistic action from these two organisms when combined. This result is in keeping with that obtained from the use of *H. pertussis* vaccine combined with either diphtheria toxin alone, or with combined diphtheria toxin and tetanus toxin.[12] Our findings are at variance with the opinion of Sauer,[13] who feels that addition of *B. parapertussis* to pertussis vaccine would decrease its potency against whooping cough and would be inadequate to protect against parapertussis.

Our previous work and that of others has shown that high opsonocytophagic indices are a definite indication of immunity. Since it is well established that immunity to whooping cough can be produced from the proper use of vaccine, it appears probable that the high index produced by *B. parapertussis* vaccine indicates that immunity to this disease can also be conferred by vaccination.

Although parapertussis has been generally believed to be a mild and innocuous disease, the recent report of Zuelzer and Wheeler[14] of two proved deaths in infants from parapertussis pneumonia shows that this disease can be of major importance.

From our studies we believe that immunity can be established against parapertussis, and we suggest that vaccines given to infants to prevent whooping

cough should also contain *B. parapertussis* vaccine. It is not unlikely that many so-called failures after pertussis vaccine will be prevented by the use of a combined vaccine.

The *H. Pertussis* Phase I organisms used for the Opsonocytophagic Test were supplied by Dr. Louis Sauer; the *B. parapertussis* organisms were supplied by Dr. Pearl Kendrick.

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ALLERGY AS A CAUSATIVE FACTOR OF FATIGUE, IRRITABILITY, AND BEHAVIOR PROBLEMS OF CHILDREN

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THE tired, listless, irritable child has long been a difficult problem for the physician, particularly the one with associated abnormalities of behavior but without obvious physical findings. Among the various causes of this condition, allergic disease has not had the recognition or emphasis that it deserves in view of its frequency as an etiologic mechanism. In this respect, allergic children are commonly misunderstood by their parents and teachers as well as by their physicians. The manifestations of fatigue and irritability in children with chronic allergic disease are similar to those occurring in adults.[1]

The allergic fatigue syndrome of children, as this clinical entity might be called, is not new. Hoobler[2] in 1916 and Laroche and associates[3] in 1919 referred to it briefly but it remained for Shannon[4] in 1922 to give the first clear description in the medical literature. He discussed the similarities of the manifestations of the neuropathic and exudative diatheses, pointing out that allergic children were restless, irritable, unruly, peevish, out-of-sorts, high-strung, and difficult to manage. He made the advanced conclusion that many of the symptoms of the neuropathic diathesis in infants and children are not infrequently the results of irritation of the nervous system resulting from anaphylactic reactions to food proteins to which the patient has become sensitized.

Rowe[5] is credited with a clear description of this clinical picture in 1931, stating that food allergy in childhood is commonly associated with restlessness, incorrigibility, bursts of temper, drowsiness, sullenness, depression, somnolence, and marked changes in disposition.

Of considerable historical interest is an excellent description of fatigue in conjunction with what appears in retrospect to have been allergic symptoms written by an educator, Smith Baker[6] in 1898, long before the recognition of clinical allergy disease. Baker clearly differentiated normal or physiologic fatigue from abnormal or pathologic fatigue, emphasizing that children readily recover from the former but that it is a question whether a child ever fully recovers from the latter. He mentioned the possible role of heredity in the production of this picture and minimized the effect of overwork or studying too hard. He also emphasized the fact that abnormal fatigue was a very serious matter and that the children so affected were in consequence always below par in every physical and mental respect. In characterizing such children, Baker drew attention to the tendency for the eyes to wander or "fix" nowhere and the fullness or blue discoloration beneath the eyes. As this excellent early

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description has not been referred to in current medical literature, it seems desirable to quote the following exerpts:

"With such children all the bodily positions are apt to be awkward and 'lopping,' with the head bent forward and the shoulders held at different heights; while the movements are very generally asymmetrical, forceless, and few in number, and are perhaps jerky, or fidgety, or irritable, from unnatural increase of reflex activity. Also the fingers are apt to twitch, the face to be stolid, the tongue to be waywardly nimble, or else perhaps absolutely unresponsive and inactive, and the speech and voice noticeably altered in pitch and volume. The 'neurasthenic voice,' once recognized, is a valuable and reliable criterion. Headaches are often complained of. These may be owing equally to eye strain, bad ventilation, starvation or poisoning, overtire, or to disease; while the subject, instead of acting naturally in common matters, trifles with his luncheon, dawdles over every task, and engages in sports, if at all, with little or no zest or skill. Upon inquiry, it will be found that he usually sleeps poorly, has nightmares, or grinds his teeth, or talks much, or 'flops round' while sleeping. Also that he emaciates rapidly and easily, and has frequent inexplicable sick-spells; that in the morning he is irritable, cross and hysterical. Investigated more closely still, it often appears that such children cannot concentrate the attention for any length of time, and cannot associate images and ideas well enough to learn much or to retain what they do succeed in learning; also that they are mentally irritable and give evidence, even when very young, of a sense of nervous tension as well as of 'ill-being.' Sometimes they become morbidly dreamy, introspective, self-depreciative, . . ."

"At this point they are apt to become fretful, perverse, sleepless, and to have all manner of "morbid fears' and feelings and ere long to become depressed, hopeless, and utterly lethargic. Certainly the danger point is not very far off now. For, in due time, there will supervene what have been called the three 'cardinal symptoms' of danger which all, whether old or young, should heed; namely: a very deep sense of misery in the morning, one or more 'insistent ideas' which cannot be thrown off, and finally so thorough a wearing out that the subject becomes anesthetic to his fatigue—that is, he is so weary that he cannot feel his own weariness."

The Tired Child was the name of a book written by Max and Greta Sehan[7] in 1926. Although none of the illustrative cases were recognized by the authors as allergic children, it is quite apparent from the description of headaches, nasal symptoms, and wheezing existing in several cases histories, that in many instances allergic children were being described.

In more recent years Rowe[8] has continued to stress changes in the personality and behavior of allergic children and similar observations have been made by Rogerson,[9] Stokes and Beerman,[10] Todd,[11] Clarke,[12] and others.

Parents are puzzled by the development of spells of "dopiness," listlessness, and sleepiness in a previously healthy, well-adjusted, and apparently normal child. They notice that at certain times and for no apparent reason the child is more irritable and "on edge" than at other times. During such periods he does not make his usual satisfactory adjustment either to his parents or

playmates, being quarrelsome, negative to suggestion, and, in general, "difficult to handle." When present in intermittent periods, these symptoms do not attract particular attention, usually being ascribed to tiredness or simply an off day. However, even at this time the alert mother may notice that these spells begin with a lustreless, watery character of the eyes associated with an edematous discolored appearance of the infraorbital areas. The upset may persist for only a few hours or for several days and may or may not be associated with some more easily recognizable allergic reactions such as rhinitis, coughing, headache, abdominal distress, diarrhea, or even urticaria or eczema.

The parents are more disturbed as the fatigue, listlessness, and irritability become more chronic, fearing the resultant effect on the child's personality. The problem appears to be accentuated by the application of more strict disciplinary measures. Many such children become so refractory to suggestion that their parents find it expedient to make suggestions in reverse.

These children are commonly restless sleepers, either crying out at night or turning and tossing in their sleep. Night sweats are not infrequent and enuresis is sometimes observed. It becomes increasingly difficult to awaken the child in the morning, and after arising he is apt to be the most fretful and irritable of any time during the day, commonly refusing to eat breakfast. One conclusion reached at this point is that the child needs more rest, but increased hours of sleep or the use of sedatives does not improve the condition. The failure of this type of fatigue to be relieved by the usual or an excessive amount of rest characterizes the condition.[1]

The parents are further concerned when they find that the child's schoolwork is not going well. Upon consultation with the school to determine the cause of the trouble, they learn that the teacher has difficulty in attracting the child's interest or maintaining his attention. Instead, he is inclined to sit and stare in a listless, dreamy fashion, or to be abnormally restless and jittery. He commonly has no desire to compete with other children in school work or in play, preferring to remain quietly by himself.

There is a wide difference in the reaction of parents to this situation. Unfortunately, a common reaction is to assume that the child is a "naughty brat" and to inflict various types of punishment to induce the child to "snap out of it." Needless to say, this approach does not help an already difficult problem. Others assume that the child must be sick and seek medical advice. In general, teachers are apt to be more alert in recognizing this type of illness than are parents.

The results of a medical study will depend upon the interests and abilities of the pediatrician conducting it. If the proper questions are asked one frequently finds some evidence of allergic disease in the past or present history. However, the more commonly associated manifestations, allergic rhinitis, allergic headaches, and gastrointestinal allergy, may either be overlooked or attributed to other causes, such as infection or nervousness.

Clinically, these cases fall into two approximate groups: the first and larger group, as illustrated by the following three cases, is characterized by the tired, sluggish, and dreamy child, who is sometimes actually depressed. The

second group, of which the fourth case described is an excellent example, is typified by the hyperkinetic, excitable child. Schneider,[13] in 1945, gave an excellent description of the hyperkinetic child and stated that it is possible that too little attention is given by the general physician and pediatrician to the role of allergy in causing or accentuating this type of reaction.

Many symptoms, particularly the irritability, the tendency to develop problems of behavior, and the poor school record resulting from difficulty in concentration, maintenance of attention, and memory are common to both groups. Some cases do not fall precisely into either group, having the clinical features of both or at different times reacting first as one type and then the other. In this connection, Stokes and Beerman[10] claim that many of the children described by parents or teachers as restless, overactive or high-strung, appeared when first seen to be quiet and subdued. Only later in watching them closely were the authors able to observe the underlying restlessness.

The following four patients were brought to the writer for help, with abnormality of behavior as their major complaints, although each had some other manifestation of clinical allergy. These cases are selected because of the clear-cut characteristics and the absence of other contributing causes of fatigue and weakness. It should be pointed out that many other allergic children have more borderline or complicated problems, but, on the other hand, there are many children with chronic allergic disease who are singularly free from the constitutional manifestations herewith described.

W. U., male, aged 8, had been subject to intermittent night sweats and bouts of unexplained fever and delirium in early childhood. Because of mouth breathing and progressive nasal obstruction, an adenoidectomy and tonsillectomy were done at the age of 3½ years. In the subsequent two years, progressive fatigue, listlessness, irritability, crankiness, and numerous minor behavior problems developed. He became negative to suggestion. Having no desire to compete with other children, he preferred to remain quietly by himself. His teachers commented on his restlessness, jitteriness, inattentiveness, and apparent difficulty in concentration.

Because of increasing deafness, he was subjected to a second adenoidectomy at the age of 5½ years. Although this relieved the hearing difficulty, it had no effect on his fatigue and related symptoms. He also had had intermittent pruritus for many years but no true dermatitis. Following mumps, his fatigue and nasal symptoms became accentuated and for the first time were associated with nocturnal coughing. His teacher suspected that his poor health had a direct bearing on his unsatisfactory school work.

His physical examination was negative except for moderately pale, boggy, edematous, nasal mucous membranes, although the nasal secretions were negative for eosinophiles. The child appeared distinctly listless and depressed on his first office visit.

Skin tests with inhalants were negative except for a positive cutaneous reaction to Endo house dust. However, there was no clinical evidence of dust sensitivity, and specific avoidance and treatment failed to relieve his symptoms.

The coughing, previously present nightly, ceased on the third day of wheat avoidance in preparation for an individual feeding test with wheat. His teacher commented that he had been less jittery and jumpy on the third and fourth days of wheat elimination. An individual feeding test with wheat, according to the technique previously described[14, 15] was followed by a return of coughing and restlessness the night of the test. The leucocyte response of this test as well as the compatible reactions with milk, eggs, and corn performed on subsequent days are shown in the first four graphs on the left of Fig. 1. Symptoms were not associated with any of the latter tests.

The continued avoidance of wheat resulted in complete relief of his respiratory and fatigue symptoms. He became much more agreeable in the home and developed increasing self-confidence and self-reliance. He had no troublesome symptoms during the summer of 1945 while following a wheat-free diet. On the return from summer camp he began eating corn on the cob daily, as many as three or four ears per meal, in spite of previous instructions to use corn sparingly in view of the obvious sensitivity to the botanically related wheat. On the fourth day of this program his mother noticed a gradual return of his rhinitis and irritability in spite of the rigid avoidance of wheat. By the end of ten days he had developed typical atopic dermatitis of the antecubital areas.

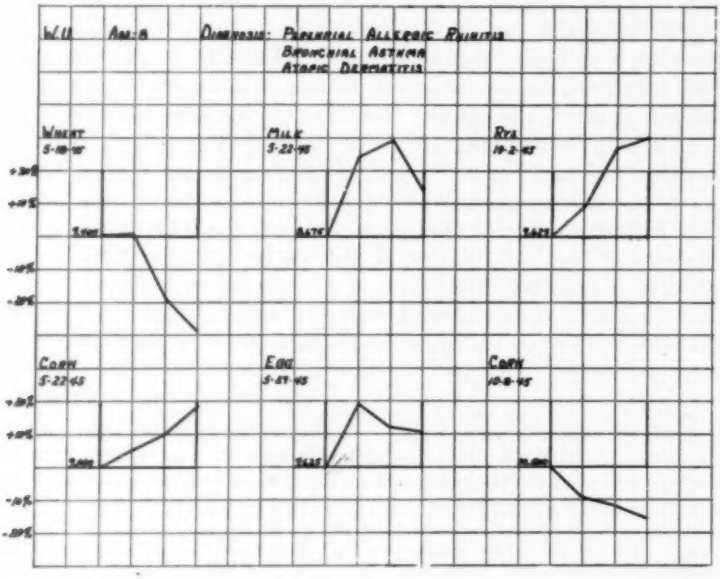

Fig. 1.—The leucocyte response in individual feeding tests in Case W. U. The post-ingestive leucocyte values are plotted in terms of their percentage variation from the pre-ingestion level.

Individual food tests were then performed with rye and corn. Although the corn test was not associated with an observable accentuation of symptoms, the leucopenia that developed (see right side of Fig. 1) was in striking contrast to the corn test four and one-half months previously. The dermatitis, rhinitis, and irritability subsided with the avoidance of both wheat and corn.

He had a similar recurrence of eczema during the 1946 corn season which was similarly relieved by the avoidance of corn. With continued restriction of wheat and corn he has had no serious allergic symptoms since this time.

In this case there is evidence that sensitivity spread from wheat to corn in as short a period as four days following the repeated ingestion of large doses of corn on the cob. The difference in the total leucocyte values following the corn tests prior to and after the development of sensitization is of particular interest.

J. C., male, aged 9 years, was first seen in late September, 1945, complaining of a persistent, hacking cough of two weeks' duration and perennial nasal stuffiness and rhinorrhea

for the past two years, slightly accentuated during the ragweed hay fever season each year. His parents had noticed a progressive listlessness and lack of interest in his surroundings coincident with the duration of his nasal symptoms. His teachers found him a difficult child to understand. They commented in his school reports on his negative attitude, inattentiveness, dreaminess, and tendency to stall and to make excuses.

Examination revealed a normal appearing child except for a sallow complexion and a listless expression. The nasal mucous membranes were boggy and edematous in type and the nasal secretions contained 40 per cent eosinophiles. Other physical and laboratory findings were negative.

Food sensitivity was not suspected by the parents.

There were positive skin tests with ragweed pollen, house dust, and cat dander. Elimination of the cat, avoidance of massive dust exposure, and treatment with house dust and ragweed extracts (based on the titrated degree of specific sensitivity), although effective in partially relieving the respiratory symptoms, did not change the chronic tiredness and listlessness. Individual feeding tests were then performed with several major foods. He developed a striking and sustained leucopenia (reaching a maximum of 25 per cent) after the experimental feeding of both wheat and corn, although he failed to develop an accentuation of symptoms during or following these tests. The individual feeding test with milk resulted in a normal postprandial leucocytosis, without associated symptoms, that with egg was indeterminate hematologically and also without associated symptoms. Eggs and other major foods except wheat and corn were ingested in cumulative feedings without accentuating symptoms.

With continued inhalant treatment and the avoidance of wheat and corn (beginning in November) the coughing and rhinitis subsided completely. Immediately after the elimination of allergenic foods the child became more alert and attentive, developing an active interest in his school work. His teacher reported that he had made one of the most startling improvements in his schoolwork during the following three months that she had ever observed. She mentioned particularly the improvement in his "nervousness" and "jitteriness," and the fact that he applied himself much better and seemed happier and more contented.

The family then became somewhat less careful in his wheat and corn avoidance and as a result he became more "growly and lackadaisical." After several repeated errors in his elimination of corn, the importance of watching his diet closely was impressed on everyone concerned, but apparently as a result of incomplete avoidance he greatly enhanced his degree of corn sensitivity. The absolute and complete abstinence from corn is now necessary to relieve this child's symptoms. This excludes corn as such, corn oil, corn starch, and particularly corn sugar (dextrose, glucose and cerulose). The small amount of corn in commercial candy, chewing gum, or commercially canned fruit is sufficient to precipitate mental and physical sluggishness and marked irritability. On repeated occasions his mother has been able to tell when he has eaten candy containing corn by the lustreless appearance of his eyes and his general listlessness. Corn-free candy containing chocolate and cane sugar, corn-free chewing gum, and fresh or water packed fruits are tolerated without symptoms.

Aside from having moderate hay fever symptoms during the 1946 ragweed season, and failing to follow his diet on a few occasions, he has remained more lively and responsive during the past year and one-half than at any time in the preceding two years. He is no longer irritable and crabby, and appears to be a happy, well-adjusted child.

When this child was first seen, a relatively low degree of sensitivity to wheat and corn existed, as shown by the failure to precipitate symptoms in association with the individual feeding tests. In both instances, specific sensitivity was suspected on the basis of the leucopenia developing after test feeding, and was confirmed by the production of symptoms after several successive meals of each food. These are excellent examples of the cumulative type of food reaction with symptoms not associated during the initial individual food tests. In the case of the corn, the degree of sensitivity became greatly enhanced, apparently as the result of incomplete avoidance over a period of time.

R. H., male, aged 8 years, had had mild postauricular eczema as an infant, chronic nasal stuffiness, and rhinorrhea since the age of 3 years. Although the nasal symptoms were accentuated from mid-July through the summer months, they persisted perennially. He had also been subject to mild asthma intermittently since pneumonia in early childhood. In recent years the manifestations of asthma had been limited principally to coughing.

In addition, he remained dopey and sluggish most of the time and he apparently tired more easily than other children. His mother claimed that he commonly went to bed on his own volition in the middle of the day. She had also noticed an increasing degree of irritability, crankiness, and refractoriness to suggestion. His schoolwork had shown a steady deterioration during the past year; his teacher claimed that apparently he was trying diligently but that she had great difficulty in obtaining his interest or maintaining his attention. He preferred to remain by himself and daydream instead of participating in the group activities of the school.

The parents did not suspect sensitivity to foods or other allergens.

Physical examination revealed a listless but well-developed child. The nasal mucosa was thickened, pale, and boggy, and the nasal discharge contained 90 per cent eosinophiles. His remaining examination and laboratory studies were negative.

Although highly sensitive to house dust and alternaria, hyposensitization failed to relieve his "toxic symptoms." Specific inhalant treatment was continued during the study of food sensitivity.

An initial high degree of corn sensitivity was determined on the response to an individual feeding test with corn meal and corn syrup. During the test he cleared his throat repeatedly, complained of marked tickling of his nose and throat, became nauseated, and vomited one hour after the initial feeding. He developed a sustained leucopenia after both the corn and wheat tests, although the latter was not associated with demonstrable symptoms. It was subsequently determined that wheat could be tolerated in spaced feedings (once in three days) but its cumulative ingestion (successive meals) produced allergic symptoms. He has been followed on this plan for the past year and his degree of wheat sensitivity has decreased to the point that it is now tolerated once daily.

With the continuation of inhalant therapy, the complete elimination of corn and the use of wheat once daily, he had complete relief of rhinitis, coughing, and fatigue for a period of four months, during which time he regained six pounds in weight. At this time his mother claimed: "He is a changed boy." A prompt improvement in disposition occurred following the institution of the therapeutic diet; he lost his former irritability, stubbornness, and disinclination to compete and play with other children, and, in turn, became much more cooperative both in the home and the school. His mother claimed that he was more calm and less nervous than previously. The child appeared to look much better in the opinion of everyone who had previously known him. The most striking change in his appearance was the result of his eyes having lost their former watery, listless characteristics.

In spite of continued inhalant therapy, he gradually had a recurrence of fatigue and listlessness in recent weeks. It was then learned that occasionally he had been eating ice cream and commercially canned fruits. Inasmuch as the first few doses were tolerated without apparent symptoms, these had been continued in his diet at more frequent intervals coincident with the redevelopment of nasal stuffiness and fatigue symptoms. With the avoidance of all sources of corn sugar these symptoms again cleared completely within a period of four days.

After the smoldering allergic symptoms had been relieved, it was then noticed on three different occasions that he had a recurrence of irritability and coughing during the night after eating commercial nonchocolate candy containing corn sugar. The absolute avoidance of corn, as previously outlined, and the continuation of inhalant therapy were necessary for complete relief of the fatigue picture and other allergic symptoms.

The last two cases illustrate the fact that the complete avoidance of all sources of corn is necessary for the control of a high degree of corn sensitivity.

In spite of the difficulties of this program, it is the ideal way to handle a corn-sensitive patient.

There has been considerable confusion in the past concerning the possible allergenic properties of corn sugars. Ratner and Gruehl[16] are of the opinion that corn syrup is nonanaphylactogenic from experimental work on guinea pigs and presumably from this evidence conclude that corn syrups and crystalline sugars of corn origin play no role in clinical allergy.

Actually, corn sensitivity ranks in incidence with allergy to wheat, milk, and eggs in the etiology of allergic manifestations of childhood as well as in adults.[17] Careful observations of clinical material reveals the unquestionable fact that corn sugars and syrups, including dextrose, glucose, and cerulose, will cause symptoms in many corn-sensitive patients. Furthermore, in many instances the corn sugars will cause a more immediate clinical reaction than will corn starch or corn as a vegetable. This is particularly true when fed experimentally under test conditions of the individual food test, all corn having been avoided for a period of four days prior to experimental feeding.

Because of the high incidence of sensitivity to corn existing in infancy and childhood, one must raise the question of whether we should continue the current vogue of relying principally on corn sugars as sources of carbohydrate in infant feeding. The less allergenic sucrose of cane origin would appear to be preferable in this respect.

T. D., male, aged 8 years, had never been a good-natured child, remaining cross, irritable, and out of sorts since infancy. His mother claimed that he acted as if he were excited all the time, talking rapidly and incessantly in a loud, shrill voice and jumping about with endless activity. He became a major behavior problem in the home, school, and neighborhood. Any attempt to discipline him resulted in fits of crying and depression.

His teacher claimed that there was something wrong with him. Instead of "settling down" as other children did, he remained jittery and fidgety throughout the day. The child did not appear to listen or learn as well as other children; he was unable to remember points with which he was apparently familiar on previous days. The child was seen medically on the urgent request of his teacher at which time he had taken the first grade twice and was failing in the second grade.

In addition to restlessness during the day, he tossed and tumbled through the night, awakening several times each night, crying out in a highly excited and frightened manner. He had also been an enuresis problem since infancy. In the mornings he was invariably groggy and dopey but much worse certain days than others. Several times a week he awakened with a frontal headache often associated with nausea, vomiting, abdominal cramps, and diarrhea. Periods of diarrhea alternated with constipation. He frequently went to bed in the midafternoon complaining of severe head pain. His appetite was always poor for breakfast, somewhat variable for other meals. He frequently would start eating as if hungry but apparently "filled up" after a few bites and commonly flopped his head over on the table.

During winter months he had frequent "colds," each lasting four or five days and associated with scratchiness of his throat. He had the chronic habit of rubbing his nose although there was no evidence of nasal stuffiness, rhinorrhea, or sneezing except when he had one of his "colds." There was also intermittent coughing during winter months but there was no other evidence of asthma.

Examination revealed a highly excitable, hyperkinetic child weighing 61 lb. with moderate pallor and edema of the nasal mucous membranes and a lustreless, watery appearance of the eyes. The remaining physical examination and laboratory studies were negative, including a nasal smear.

Inhalant or food allergens were not suspected. Cutaneous and intracutaneous tests with inhalants were negative except for a positive intracutaneous reaction to Endo house dust. A program of avoidance and treatment with house dust did not relieve the restlessness, irritability, headaches and gastrointestinal manifestations.

Inhalant management was continued during the time diagnostic studies for food sensitivity were undertaken. On the third and fourth days of avoiding wheat in preparation for an individual food test, the child appeared noticeably happier and more agreeable. The trial feeding of wheat was associated with a recurrence of irritability and nervousness and a sustained postingestive leucopenia. He developed a severe headache within five minutes after an individual food test with corn (corn meal and corn syrup) and felt miserable for the remainder of the day. A similar reaction was reproduced after the ingestion of corn as a vegetable four days later. Compatible reactions occurred on testing similarly with milk, eggs, and potatoes.

The avoidance of wheat and corn in addition to several other regularly ingested foods resulted in the prompt relief of symptoms. All other foods except wheat and corn were returned to the diet and tolerated in cumulative feedings. With elimination of both cereal grains he began to eat better and gradually recovered from the irritability and chronic excitability. He has had complete relief of the headaches, gastrointestinal symptoms, and nightmares. The enuresis, formerly present each night, has occurred only occasionally in recent weeks, and he is still improving in this respect. His attention in school is greatly improved, as reflected in greater interest in his schoolwork and a significant improvement in his grades. The child is much more amenable to suggestion than formerly; both home and school discipline is now received in better grace, in contrast to outbursts of crying and depression formerly associated with disciplinary suggestions.

These cases are best recognized from details of their history. The physical examination of children with the fatigue picture is usually negative, particularly if the associated allergic manifestation happens to be headaches or gastrointestinal symptoms. Evidence of an allergic rhinitis is commonly not detected in an examination, and nasal smears for eosinophiles are by no means routinely performed on patients with continual "colds," and eosinophiles may or may not be present in the nasal secretions. Neither is the presence of a peripheral blood eosinophilia to be relied upon for the detection of allergic disease.[18] Although many of these children have a sallow complexion and some appear anemic, blood counts, urine examinations, x-rays, and other laboratory work are usually within normal limits.

Perhaps the most singular physical feature of these children is their facies, although this is apt to go unrecognized unless one is alert to its significance. The combination of slight degrees of pallor, puffiness of the eyes, relatively fixed facial expression, and mental dullness gives many of these children a characteristic appearance.

The eyes have a lustreless, dull quality, apparently as a result of puffiness of both lids with fullness and discoloration of the infraorbital areas. Variations in the degree of puffiness of the orbital regions are seen most clearly in the allergic individual under daily observations, as for instance, in a member of one's family. The alert and observing mother often associates the appearance of the eyes with the presence of allergic symptoms, particularly at a time when such manifestations are occurring in intermittent attacks. Not infrequently the eye findings are the only objective evidence of current allergic intolerance. Although the so-called "circles under the eyes" may result from other causes,

they have been observed to disappear in allergic individuals coincident with the institution of proper dietary management, and to reappear with experimentally or accidentally induced allergic reactions.

These tired dreamy children do not react with the changes in facial expression as one might expect in normal, well-adjusted and happy children. Many appear to be devoid of a sense of humor, moody, or dulled to the environmental stimuli that ordinarily cause reactions in children. In this connection, Todd[11] speaks of the clouded mental ability of allergic children, particularly those with gastrointestinal sensitivity. He makes the further statement: "As the allergy clears, the mental cloud lifts, and thus the child appears to increase rapidly his I.Q."

These children may or may not have the facial features as described by Duke[19] in association with nasal allergy and attributed by him to faulty development of the paranasal sinuses, or the facial and dental deformities described by Bowen and Balyeat.[20]

In the absence of outstanding positive findings as a result of the physical examination and laboratory information, and in the presence of the maladjustment which commonly exists between a sick, fretful child and his parents or teacher, the physician commonly assumes that the child's abnormalities of behavior are of psychic or emotional origin. In individual cases, this may be the correct explanation, but it may also be most misleading, particularly in instances where the allergic factor is not recognized. Neither may it be assumed that the existence of clinical allergy and nervous manifestations in the broadest sense are mutually exclusive, as any chronic illness is quite apt to be complicated by a significant psychogenic component. The differential diagnosis between fatigue, irritability, and abnormalities of behavior of allergic versus nervous origin is rendered difficult by the fact that both conditions have several descriptive features in common, a point of view first stated by Shannon[4] in 1922 but which has received relatively little subsequent emphasis. In instances where both factors apparently exist, as one might expect in the majority of advanced cases, the significance of the nervous element may be judged more correctly after a proper attempt has been made to diagnose and control the allergic factor. The psychic and emotional features of these cases were not probed initially, in view of the clear-cut relationship of symptoms following the test or cumulative ingestion of specific foods and relief of symptoms as a result of allergic management.

One might say that the attitude of parents changed when they learned that their child was actually sick instead of naughty and that the improvement in the child's behavior was the result of this altered reaction or a greater insight on the part of the parents. This point is obviously important and cannot be completely controlled. However, it is not necessarily advantageous to the child in so far as the child-parent relationship is concerned. For instance, Forman[21] stressing the importance of mental hygiene in the management of the behavior abnormalities of allergic children, feels that the mother's overprotection of the sick child is a major factor in the child's improper adjustment. In view of the heredity of allergic disease, one commonly is not dealing with normal par-

ents. Todd[11] commented on the fact that nervous tension, distractibility, restlessness, short attention span, irritability, whining, and proneness to fatigue of allergic children are often serious domestic problems, especially when the parents, themselves affected with allergy, have not too large a stock of patience or tolerance for the exasperations induced by the conduct of the child. In the present series, as well as in the majority of other allergic children studied, the child-parent relationship cannot be considered as the major factor in the genesis of these disturbances in view of the intentionally or accidentally induced recurrences of irritability and abnormalities of behavior associated with the incomplete avoidance of specific food allergens.

Again, one interested in psychiatry might say that the special tests and dietary maneuvers through which both parents and children are placed constitutes a psychotherapeutic approach in its own right. This cannot be denied and neither can it be controlled under the conditions existing in the practice of medicine. Speculative arguments of this type come up against the hard and fast fact that recurrences of irritability and abnormalities of behavior in these children may be induced experimentally.

The four cases reported have the common features of occurring in boys of similar age who were sensitive to both wheat and corn. Children of any age may be affected by this type of reaction. Although it is more frequently the result of sensitivity to wheat or corn or both, it also may be due to allergic reactions to milk, eggs, potatoes, orange, or any other food or foods eaten in oft-repeated feedings. Shannon[4] also found a high incidence of wheat sensitivity. Allergy to corn is emphasized in this discussion not only because it so frequently produces this clinical picture, but because it is by all means the most difficult food for a child of this age to eliminate, and, consequently, because corn sensitivity is very frequently not diagnosed.

It should be noticed that three of the cases were complicated by clinical evidence of inhalant sensitivity and that the fourth had skin-test evidence of house dust sensitivity. In no instance, however, did specific inhalant therapy relieve the constitutional symptoms which prompted the medical consultations. Inhalant allergy may be responsible for similar fatigue symptoms; this is seen not infrequently in cases of severe hay fever and was first pointed out by Kahn.[22] Persistent perennial symptoms, such as existed in the cases herewith reported, are usually the result of food sensitivity. Because of the frequent co-existence of inhalant and food allergy, however, all cases should be controlled from the standpoint of inhalant sensitivities before undertaking the diagnosis of food allergy, for otherwise one may be confused by the presence of inhalant symptoms during clinical tests for the detection of specific food sensitivity.

The clinical picture, emphasizing the behavior aspects of allergic children, is typical of the smoldering reactions of masked food allergy, a term coined by Rinkel[23] to describe the chronic symptoms resulting from the frequent ingestion of allergenic foods. Actually, an individual often feels better immediately following a meal containing a masked food allergen, the delayed accentuation of symptoms occurring prior to the next meal or during the night. As the smolder-

ing delayed effects of a single feeding may persist for as long as four days, during which time several additional feedings are usually eaten, it makes it highly improbable that a child or his parents will suspect sensitivity to a food eaten several times daily. In this connection it is of interest that sensitivity to wheat or corn was not suspected in any of the four cases presented.

However, when such a food is eaten under the conditions of the individual food test, that is, experimental feeding under observation following four days of abstinence of the food in question, a diagnostic, clinical, or blood response is usually obtained.

In this respect it should be re-emphasized that the recognition of a specific food sensitivity is still a clinical problem, skin testing notwithstanding. Cutaneous or intracutaneous skin tests with the common food allergens were not performed in this series or in other cases studied for food allergy in the past five years because of the unreliability of these procedures in detecting the presence or absence of current specific sensitivity. On the other hand, skin test results with inhalant allergens are highly reliable and constitute an essential part of any allergic investigation.

If elimination diets are used as diagnostic measures, it is imperative that all sources of corn be completely eliminated. (The Rowe Elimination Diets[24] are not entirely corn-free in their present form.) One must remember that specific food allergy cannot be diagnosed as a result of improvement following the elimination of a given food, but must be confirmed as a result of returning that food to the diet, preferably under experimentally controlled conditions which permit of accurate observations. The technique of the individual food test meets these specific requirements. In the absence of accentuated or precipitated symptoms, the variation in the postingestive leucocyte values affords presumptive evidence of clinical tolerance or intolerance.[15]

SUMMARY

The fatigue syndrome of allergic origin is a common cause of irritability and abnormalities of behavior in children. It usually results from chronic food allergy involving sensitivity to more than one food. Although any food ingested in oft-repeated feedings may be the cause of such chronic symptoms, sensitivity to wheat and corn is encountered most frequently.

Clinically these cases fall into two groups; first, the chronically tired, sluggish, and depressed child, and second, the hyperkinetic and hyperexcited child. Both are inclined to be irritable and fretful in their behavior and to be maladjusted in both the home and school. Their schoolwork suffers because of a characteristic difficulty in concentration and impairment of memory.

Although this clinical picture may be the sole allergic manifestation exhibited by a child, it is more commonly associated with a history of one or more other expressions of clinical allergy.

These children are most commonly considered as "nervous," a point of view that is not particularly helpful in their treatment. The striking similarities between the so-called "nervous" child and the allergic child are noted.

When dealing with allergic children, the significance of psychic and emotional factors in the genesis of irritability and behavior problems may be judged to best advantage after the allergic reactions are brought under control.

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Case Reports

CONGENITAL HUMERORADIAL SYNOSTOSIS WITH OTHER SYNOSTOTIC ANOMALIES

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CONGENITAL fusion of the bones of the appendicular skeleton is rather infrequent, according to a review of the foreign and domestic literature in 1944 by Murphy and Hanson.[1] They found only twenty-four cases of congenital humeroradial synostosis reported, most of them in the European journals. Murphy and Hanson report the twenty-fifth case. The addition of another case (the twenty-sixth reported case) should be of interest, particularly because of the other anomalies of bone and joint formation.

Fusion may take place at any point where bone tissues are adjacent to other osseous members.[2] The cause of fusion is to some extent obscure. At least two means of production seem possible. The cartilagenous formation which precedes bone development in the fetus may fail of proper segmentation or, after segmentation has occurred, fusion may take place. Undersegmentation and excess segmentation both are possible. Either malformation may be in a transverse or a longitudinal direction with respect to the member involved. Undersegmentation produces a reduced number of bony parts, and the case reported is of that variety, with the fusion transverse in each instance, osseous tissue which ordinarily forms two or more bones being united into one rigid mass. Deformities of this nature seem to be more prevalent distally and as a rule produce less disability in the peripheral regions. There is a difference of opinion regarding bilateral involvement, but comment on this point seems to indicate that bilateral involvement predominates. If bilateral involvement is found, the disturbed formation is often symmetrical. It should be noted that many patients show deficiencies of distant and unrelated tissues, so that the life expectancy is decreased, although no evidence of such a situation has appeared in the case reported. One writer suggests an attempt in this manner by nature to prevent reproduction of other malformed individuals. A marked familial tendency also exists, suggesting a hereditary factor. One report mentions humeroradial synostosis in four of seven siblings which also indicates that if hereditary, it depends upon a dominant trait. No external cause has been reported and no exogenous etiologic factor seems probable. A significant sex trend is not evident in case reports.

The extent and type of disability produced depends upon varied factors, such as the location and angle of fusion and, obviously, the number of bones or joints involved. Some of the fusions of the humeroradial area are at an angle of 90 to 120 degrees, which is near the optimal angle for artificial fusion and produces similar disability. Murphy and Hanson have reported a patient with the angle being about 90 degrees. It has been learned that the mother of that patient has given birth to another infant with humeroradial synostosis, the angle of fusion being 45 degrees.[3] In such a case, the range and extent of motion is quite limited. Also, when the extension at the elbow is much greater than

Case reported at the Goodrich General Hospital Staff Meeting of November, 1946.

120 degrees, many motions may be difficult or impossible, motions of eating, dressing the hair, and adjusting the clothing in the upper midline being of importance.

With fusion and continuous osseous tissue from shoulder to wrist (as here reported), growth in length will be reduced as no epiphyses appear possible at the elbow in the two bones now fused. An unequal length of the ulna as compared to the radius with the ulna free to grow may produce one of three situations: (1) extension of the ulna proximally at the elbow; (2) extension distally at the wrist; or (3) curvature of the ulna. Pronation and supination of the hand is impossible. When deformities are present in addition to that at the elbow, they may be of greater importance, particularly as in the reported case, where the angle is nearly optimal at the elbow and the other rigidities are numerous and involve all of the digits. The disturbance of growth in length and the failure of muscular development due to disuse are of great import.

Fig. 1.—The malformation of the hands and feet is shown, as has been enumerated in detail.

The literature is ominously silent with regard to results of definitive treatment. Surgery was attempted in one case but results are not given.

PRELIMINARY REPORT OF A CASE

Mrs. L. W. entered the hospital, October 2, 1946. She is a white, adult female, aged 18 years, well developed and nourished, gravida I, at term. Pregnancy had been uneventful. Subsequent inquiry showed that L. W. required a special shoe for one foot during several years of her childhood. Careful question-

Fig. 2.

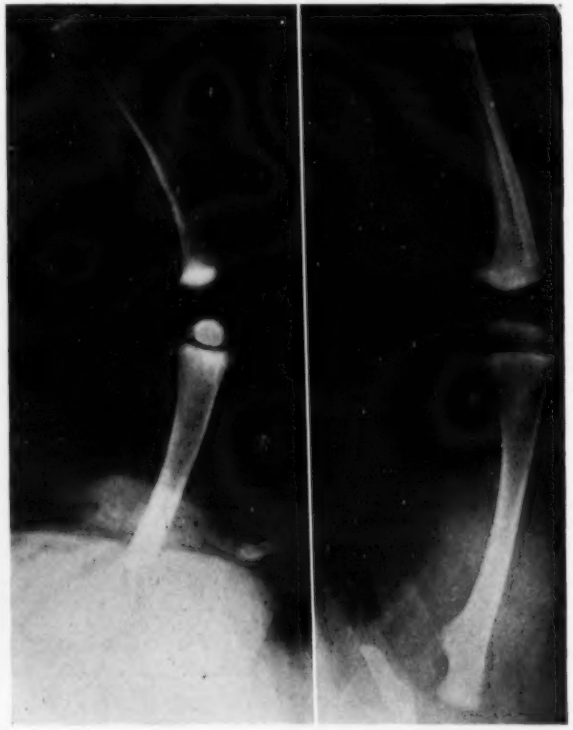

Fig. 3.

Fig. 2.—The formation at the right elbow shown in anterior and profile projections.
Fig. 3.—The right leg shown from two angles. The anterior convexity of the tibia is obvious.

ing showed that no similar deformity existed among the siblings of L. W. or her husband, nor among the ancestors, paternal or maternal, for two generations. After a labor of normal length and force, a female infant was delivered. The cardiac and respiratory responses were satisfactory. A slight inversion of the feet was evident, but the range of motion seemed approximately normal. The elbows were flattened in a lateral direction and the elbow showed a prominence at the site of the olecranon. The elbow resists motion of flexion, extension, and rotation, being entirely rigid. The angle of the forearm on the arm is about 110 degrees. The hand is in midposition as regards pronation and supination. The fourth toes are not protected by nails. The digits of the hands and feet show extensive malformation which is bilaterally symmetrical and to some extent similar in the upper and lower extremities. The accompanying photograph shows the deformities rather clearly.

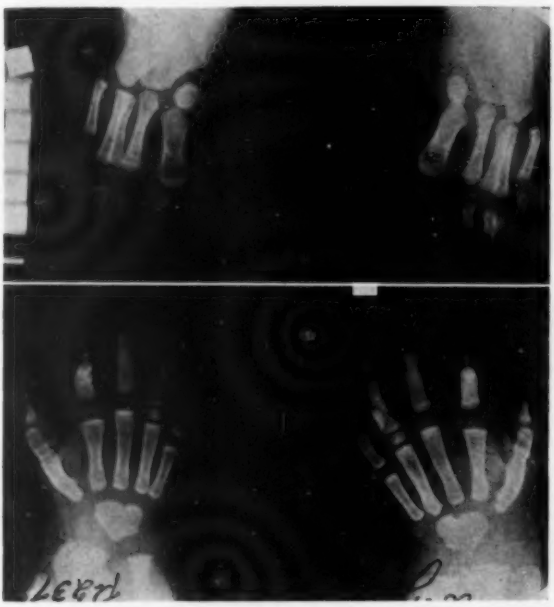

Fig. 4.—More detailed x-rays of hands and feet, showing the fusion of carpals, metacarpals, and phalanges.

Careful inspection of the hands and feet shows: (1) rigidity at the elbow at an angle of 110 degrees, the hand in a position midway between pronation and supination; (2) rigidity at the region of the metacarpophalangeal joint of the thumb; (3) rigidity of the index finger at the regions of all interphalangeal joints; (4) rigidity of the third and fourth digits at the regions of the metacarpophalangeal and all interphalangeal joints; (5) rigidity of the fifth finger at the region of the metacarpophalangeal and proximal interphalangeal joints; (6) The rigid joint regions are in a position of extension while the nonrigid joints are rather acutely flexed.

As has been stated, the hands are similar to each other and there is also a lesser though marked similarity between the upper and lower extremities. It is of great importance that the arrangement of the thumb, the index, and the fifth

fingers is such as to permit the apposition of their distal ends. If this favorable situation continues, many of the finer prehensile functions will be possible. Forceful efforts will be more limited.

It is difficult to predict what limitation of function may result in the lower extremities. A curvature of the tibia convex anteriorly is shown by x-ray. Probably the condition is minor compared to the other malformations.

A roentgenographic study of the extremities was made at 6 months. These show that certain of the rigid areas are not ossified, but are in a cartilagenous state. The rigidity and the lack of epiphyses in these regions indicate future bony fusion as ossification matures. The appearance of the bony structures at the elbow as well as at some other points is one of continuous osseous tissue with no semblance of a joint suggesting that the fusion is of long standing in fetal life. The single large mass of osseous tissue in the carpal regions probably means limitation of motion eventually in that region.

RADIOLOGIST REPORT

Examination of the upper extremities. There is a congenital fusion between the lower end of the humerous and the upper end of the radius on both sides. In the carpal region there is a large, irregularly shaped bony structure; there is a fusion between the first metacarpal and the proximal phalanx of the corresponding digit, a fusion of the proximal and middle phalanges of the index, middle, ring, and little fingers, and in the region corresponding to the epiphysis of the head of the fourth metacarpal is seen a large bone structure which is probably a separate ossification center, whereas the ossification centers for the epiphyses of the second, third, and fifth metacarpals are barely visible (Fig. 1). These changes are symmetrical.

Examination of both lower legs (Fig. 3) shows no definite changes from the normal, except some anterior bowing of the upper third of the tibia on both sides. Examination of the feet: there is only one definite phalanx of the great toe, although a large, rounded bone may represent the proximal phalanx; there is an apparent fusion of the proximal and middle phalanges of the second, third, fourth, and fifth toes; there are very tiny calcified shadows at the tips of the second and third toes which may represent the distal phalanges novisible on the fourth and fifth toes. These findings are symmetrical on both sides.

SUMMARY

The twenty-sixth case of humeroradial synostosis is reported, which shows, in addition, numerous other bone and joint anomalies. Some points of etiology and frequency are briefly discussed. This is a preliminary report of the case at the age of 6 months. No treatment has been suggested and none has been undertaken.

X-ray interpretation and films by M. W. Clift, M.D., roentgenologist, Hurley Hospital, Flint, Mich.

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DELAYED EXHIBITION OF ERYTHROBLASTOSIS FETALIS AFTER EIGHT NORMAL PREGNANCIES

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THE irregular occurrence of erythroblastosis fetalis in the face of maternal and fetal Rh incompatibility is well known. This inconsistency is ascribable to a number of factors, among which the parity of the mother is important. The offspring first afflicted in involved families is reported to be modally the third or fourth in a sequence of pregnancies.[1] The condition may, at times, appear in earlier offspring or occasionally not until after many pregnancies. This variable occurrence may be dependent on variations in placental permeability, on the capacity of the mother to form antibodies, on whether the mother is a secretor or nonsecretor, or on other factors as yet unknown.

The literature contains reports of erythroblastosis fetalis occurring late or not at all in a series of pregnancies of multiparous Rh-negative women. Cappell[2] cites four families in which the last born of nine, ten, thirteen, and fourteen children, respectively, did not manifest the disease, although they were Rh positive and the mothers Rh negative. Rh typings of the fathers and earlier offspring were not reported, but all these offspring were normal. Race and his associates[3] describe two multiparous Rh-negative mothers who first gave birth to erythroblastotic infants in their eighth pregnancies; here, too, data on the Rh types of the preceding children are incomplete. Wiener and Sonn[4] record one family of an Rh-negative mother and a homozygous Rh-positive father, in which erythroblastosis fetalis did not appear until the eighth pregnancy. Cappell[1] describes a remarkable family in which the mother was Rh negative, the father Rh positive, and erythroblastosis fetalis first appeared in the fourteenth infant. Of the previous thirteen pregnancies, three had terminated in miscarriages, and ten had produced healthy, Rh-positive infants. This paper reports a similar, fully documented case, in which erythroblastosis fetalis first appeared after a long series of pregnancies producing healthy, Rh-positive offspring.

CASE REPORT

J. S., a white male infant of 6 weeks, had been born at another hospital by a full-term spontaneous vertex delivery to an Rh-negative mother who had previously given birth to eight healthy infants. At birth the infant was deeply jaundiced, failed to breathe spontaneously, and required resuscitation. The birth weight was 3,900 Gm. Examination of the infant twelve hours after birth revealed icterus, cyanosis, and generalized edema. A blood count revealed a hemoglobin of 10.5 Gm., with ninety-two nucleated red blood cells per 100 leucocytes. A diagnosis of erythroblastosis fetalis was made, the infant was given several blood transfusions, and, at the end of two weeks, was discharged from the hospital in good condition.

During the next four weeks the infant thrived, gained weight up to 4,400 Gm. but became progressively more pale. Examination on admission to the New York Hospital showed a well-developed and nourished 6-week-old infant with moderate pallor of the skin and mucous membranes, but no jaundice. A soft precordial systolic murmur was heard; the liver edge was palpable 2 cm. below the right and the spleen edge 1 cm. below the left costal margin, in the nipple lines.

Laboratory data were as follows: Hemoglobin 8.0 Gm., red blood cells 2.2 million, white blood cells 12,500, with a differential count of 53 per cent lymphocytes, 7 per cent monocytes, 2 per cent eosinophiles, 1 per cent basophiles, 26

From the New York Hospital, and the Department of Pediatrics, Cornell University Medical College.

TABLE I

Father—Group O, Rh positive.	(Hr serum was not available for determining father's Hr type.)
Mother—Group B, Rh negative.	(Anti-Rh_o titer of 1:200, six weeks after end of ninth pregnancy)
1927, F—Group O, Rh positive.	Living and well. No history of neonatal jaundice or anemia.
1930, M—Group B, Rh positive.	
1932, F—Group B, Rh positive.	
1934, M—Group B, Rh positive.	
1938, F—Group B, Rh positive.	
1941, M—Group B, Rh positive.	
1943, F—Group O, Rh positive.	
1944, M—Group B, Rh positive.	
1947, M—Group O, Rh positive.	Erythroblastosis fetalis.

per cent segmented polymorphonuclears, 8 per cent nonsegmented polymorphonuclears, 1 per cent metamyelocytes, and 2 per cent myelocytes. There were anisocytosis and poikilocytosis of the red cells, and eleven nucleated red cells per 100 leucocytes. The blood group was 0, Rh positive, and no maternal anti-Rh antibodies were found. The icterus index was 3.8 units. Examination of the sternal marrow showed a total nucleated cell count of 109,000 per cubic millimeter, with 18.5 per cent normoblasts, 1 per cent erythroblasts, 43.5 per cent lymphocytes, 4 per cent segmented polymorphonuclears, 15.5 per cent nonsegmented polymorphonuclears, 5 per cent metamyelocytes, 10.5 per cent myelocytes, 2 per cent blasts, and 11 megakaryocytes per cubic millimeter.

The infant was given two transfusions of compatible Group 0, Rh-negative blood totalling 160 c.c., and was discharged from the hospital in good condition with a hemoglobin level of 13 Gm. When the infant was last seen at the age of 3 months he was in excellent condition and had maintained a normal hemoglobin level.

Of special interest were the results of blood typing of the patient's entire family. These showed that all eight previously born siblings, none of whom had ever shown jaundice or anemia or other signs of erythroblastosis fetalis, were Rh positive. The mother's blood was Rh-negative and contained agglutinins against Rh_o in a titer of 1:200. She had never received a blood transfusion and had had no pregnancies other than those listed below. It had evidently required nine Rh-positive pregnancies to produce in her an anti-Rh antibody titer sufficient to produce erythroblastosis in the fetus. Whether the mother was a secretor or nonsecretor was not determined. The pertinent data on the parents and children are shown in Table I.

SUMMARY

A family is reported in which erythroblastosis fetalis occurred for the first time in the ninth born, although all previous offspring from the Rh-negative mother had been Rh positive. The basis for this delayed exhibition of the disease was not determined, but whatever the explanation, this case report confirms previous observations that a mating between an Rh-negative woman and a homozygous Rh-positive man may not produce an erythroblastotic infant until after many pregnancies. Knowledge of this fact may offer encouragement to Rh incompatible couples contemplating marriage.

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PROLONGED ANURIA FOLLOWING A SINGLE INJECTION OF A BISMUTH PREPARATION

Possible Response to Therapy With BAL

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TOXIC reactions to bismuth therapy are usually thought of in the light of repeated dosage over a relatively prolonged period of time. References to toxicity from single doses are rare. However, Boyette[1] has recently reported a case of bismuth nephrosis in an infant following a single dose of Thiobismol and terminating in death on the tenth hospital day. Our case is similar, though not so tragic, and is reported to re-emphasize this serious complication, as well as to demonstrate the marked degree of acute nitrogen retention which can be tolerated by a young child without associated cerebral symptomatology, and without clinically demonstrable permanent kidney damage. Possible favorable response to BAL therapy is suggested.

CASE REPORT

A 26-month-old white female infant was given an intramuscular injection of 0.5 c.c. Thiobismol (Parke, Davis & Co.) by the family physician six days prior to admission as therapy for swollen red gums. The condition had been first noted one day earlier, after three days of symptoms of nasopharyngitis. About eight hours after the injection of Thiobismol the child ceased voiding urine and was not believed to have voided again before admission to the hospital five and one-half days later. In the interim, she became progressively lethargic but took fluids in amounts estimated to be one quart per day. Vomiting occurred on only two occasions. Some twitching of eyelids was noted during the twenty-hour period prior to admission. The painful, swollen gums persisted to time of admission.

The past history and family history were noncontributory except that the child was not known to have been given any bismuth preparations before the present illness.

Admission physical examination revealed a well-developed and well-nourished 2-year-old girl who was somewhat lethargic but awake, lucid, and cooperative. Temperature was 37.3° C.; pulse 120 per minute; respiration 20 per minute; blood pressure 90/30; weight 11.6 kg. The skin was hot and dry with good turgor and no demonstrable edema. Extraocular movements were normal as were the ocular fundi. There was some mucopurulent nasal discharge. Buccal mucous membranes were injected in the gingiva. Heart and lungs seemed normal. Urinary bladder was not percussible or palpable. A congenital absence of the right forearm was noted. The reflexes were within physiologic limits except for bilateral unsustained ankle clonus. A very small amount of urine was passed during an attempted catheterization shortly after admission. The specimen was lost and no urine was obtained from the catheter. Hemogram showed hemoglobin 65 per cent, red blood cells 3,330,000 per c.mm., white blood cells 6,450 per c.mm., differential 43 per cent segmented polymorphonuclears, 2 per cent unsegmented, 45 per cent lymphocytes, 8 per cent monocytes, 2 per cent eosinophiles. The nonprotein nitrogen in the blood was *240 mg. per 100*

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c.c. Blood carbon-dioxide combining power was 25.9 vol. per cent with blood pH 7.22. Serum protein was 5.3 Gm. per 100 c.c.

Hospital Course.—During the day of admission the patient was given 360 c.c. (30 c.c. per kilogram of baby's weight) of 10 per cent glucose in water intravenously, and 270 c.c. orally. Hot stupes were applied to the abdomen. No urine was voided. Blood pressure remained around 110/70.

On the second hospital day anuria continued. Patient was irritable but quite rational and received a total of 2,125 c.c. of fluid, of which 1,425 c.c. was given parenterally. Sodium bicarbonate 1.0 Gm. every four hours was given orally to a total of nine such doses. The gingivitis was treated with penicillin mouthwashes every three hours for six days. Because in the twenty-four hours following admission the child had not voided despite a large fluid intake, and since, if the story were correct, the child had then been almost completely anuric for six and one-half days, it was determined to administer BAL. Her appearance at this time was unusually good, even though the nonprotein nitrogen was markedly elevated and the plasma bicarbonate and plasma pH were low. Three tenths cubic centimeter of a 10 per cent solution in oil of 2-3 dimercaptopropanol ("BAL"), (2.5 mg. per kilogram), was given intramuscularly every four hours to a total of six doses.

Early on the third hospital day the patient started to void and an estimated total of 570 c.c. was passed this day. The urine was acid in reaction, had the slightest possible trace of albumin, and no reducing substance or acetone. There were 3 to 4 red blood cells and 6 to 8 white blood cells per high power field. On this day the blood carbon dioxide had risen to 38.7 volumes per cent and the blood pH was 7.40. The patient was quite alert and cooperative.

Throughout the remainder of the hospital course the patient remained rational. Urine specimens contained no further red blood cells; however, there were numerous white blood cells and urine cultures were positive for *Bacillus coli* and *Staphylococcus aureus*. Urine output increased to 1,265 c.c. on the fourth hospital day and remained good thereafter, although measurement was not accurate due to incontinence. Albumin persisted in the urine until the twelfth hospital day. Specific gravity remained under 1.010 throughout the hospital course; however, a specimen obtained one week after discharge was normal microscopically and chemically with a specific gravity of 1.020.

It is to be noted how slowly the blood nonprotein nitrogen fell. The level on admission was 240 mg. per 100 c.c. On the sixth day, three full days after the child had begun to void, it was still 125 mg. per 100 c.c. and on the tenth hospital day it was 37.9 mg. per 100 c.c.

The blood pressure was elevated on admission to 110/70 and also fell gradually remaining slightly above normal as long as the eighth hospital day and the sixth day after renal function had been restored. The blood hemoglobin was observed to fall slightly from 66 per cent on admission to 53 per cent on the tenth hospital day. The white count and the differential counts remained normal throughout the hospital course. The fluid intake, output, and laboratory data are shown in the accompanying table.

COMMENT

The therapeutic agent which apparently precipitated this episode of anuria was a 10 per cent solution of sodium bismuth thioglycollate in water (Thiobismol). The usual adult dose is 2 c.c. three times weekly. This patient reacted unfavorably to the initial dose of 0.5 c.c. According to Sollmann[2] this is by far the most quickly absorbed and most quickly excreted form of bismuth used therapeutically. The channel of excretion being through the kidneys might lead one to suspect that any toxicity would be centered in that organ.

TABLE I

DAY OF ANURIA	6	7	8									
Hospital day	1	2	3	4	5	6	7	8	9	10	11	12
Clinical state	Somewhat lethargic	Rational, irritable	Alert, co-operative									
Blood pressure (mm. Hg.)	110/70	110/80	90/60	90/55	95/60	90/50	90/50	105/60	75/45	85/60	75/55	
Blood nonprotein nitrogen (Mg./100 c.c.)	240			166		125	120	83.2		37.9	44.0	
CO_2 and pH	25.9 7.22		38.7 7.4									
Output (c.c.)	30	0	570	710	1265	720	650					
Intake (c.c.)	630	2125	1030									
Urine (sp.g.)											1.010	1.005
Urine reaction			Acid				Acid			Acid	Acid	Neutral
Urine albumin			SPT				+			+	+	0
Urine RBC			3-4				0			0	0	0
Urine WBC			6-8				60-80			60-80	10-15	5-10

The "BAL" was administered in an effort to remove the heavy metal from its association with tissue proteins and thus facilitate its excretion. This action of "BAL" in arsenic toxication has been studied by Peters, Stocken, Thompson[3] and others,[4, 5] and has been demonstrated in mercury poisoning.[6, 7] It is logical that the same detoxification might be expected with bismuth. Possible effectiveness of "BAL" in this case cannot be established.

It is to be noted that anuria persisted for almost eight days following the injection of the bismuth preparation. Despite the azotemia, slightly elevated blood pressure, and low pH and carbon dioxide, the child did not appear or act seriously ill. The plasma carbon dioxide and pH responded promptly to treatment. Azotemia persisted for nine days after restoration of renal function. Subsequent examination failed to disclose any permanent damage occasioned by the prolonged anuria.

SUMMARY

1. A case of anuria of eight days' duration following intramuscular administration of 0.5 c.c. Thiobismol is presented.

2. Therapy was limited to intravenous fluids and the use of "BAL" for any detoxifying action it might have.

3. After eight days of anuria, urine output was re-established.

4. Blood nonprotein nitrogen rose to 240 mg. per 100 c.c. during the period of anuria and fell gradually to normal over a period of about ten days.

5. No apparent permanent renal injury was sustained.

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Erratum

In the article by Brines and associates entitled "The Blood Volume in Normal Infants and Children" in the JOURNAL OF PEDIATRICS, Vol. 18, No. 4, April, 1941, pages 447-457, on page 448, Table I, column 11 (Hematocrit %), Cases 47-50, should read as follows:

44.0 instead of 70.6
38.9 instead of 85.2
38.1 instead of 75.8
44.3 instead of 89.0

The authors request that librarians make this correction in library copies.

Psychologic Aspects of Pediatrics

POOR APPETITE IN YOUNG CHILDREN

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COMPLAINTS about poor appetite in young children continue to be frequent, despite a clear understanding of the mechanisms involved.

Etiology.—The period between one and 5 years is one of relatively slow growth. Whereas infants gain about 15 pounds during the first year of life, tripling their birth weight, the average annual weight gain during the next four years is only about 5 pounds. Moreover, while infants generally gain steadily, the weight gain later on is likely to be irregular, and months may pass without any increase in weight at all. Corresponding to the relatively slow weight gain, there is a lessened need for food and, in turn, a smaller appetite. Though the gain in weight is only slightly more rapid during the early school years, the need for food (and hence the appetite) is increased because of greater muscular activity.

Parents often fail to understand the reason for the lessened appetite of their children and they show their concern by pleading and, often, by trying to force them to eat.

The years between one and 5 are years of rapid psychologic development. The child is becoming aware of his environment and is becoming increasingly independent. He registers his emerging self-dependence by resisting parental direction (negativism) and by insisting on doing things in his own way (aggression).

The child of 18 months is no longer the pliable, acquiescent being that he had been a few months earlier. He now takes a certain delight in resisting his parent and in seeing her agitate herself. He may not eat even though he is hungry, simply because he has learned that in this way he can gain attention. In addition, he may use refusal to eat as a means of annoying his parents when he feels that he has been neglected.

A prominent cause of eating difficulty in young children is insistence by the parent that the child eat certain foods which she considers are "good" for him. Related errors are continuing to feed "baby foods" and failure to prepare food interestingly.

Improper training is another etiologic factor. It has become fashionable among physicians to introduce solid foods into the diets of babies before they are developmentally ready to receive them. Babies are ready to handle solid food at about 3 or 4 months of age. At this age, they start to make biting movements and are able to transfer food from the front to the back of the mouth

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with the tongue. A good sign of readiness is the response of the baby to insertion of the tongue depressor into the mouth. A young baby tries to eject the tongue depressor forcibly, making inspection of the throat difficult. The ease with which the baby accepts the tongue depressor is a good measure of readiness for solid food.

Premature attempts to feed babies solid foods are likely to be unnecessarily difficult, and hence lead to early maternal concern about the eating situation.

A common error in child training is failure to transfer from the pureed foods to the foods which require chewing. This change can ordinarily be made between 7 and 10 months of age. Children who continue to receive pureed foods too long are likely to be poor chewers. They may refuse to swallow coarse particles and they sometimes hold food in the mouth for hours, even days.

Many mothers continue to feed their children after they are able to eat by themselves. They do this because they fear that their children will eat less if they feed themselves or will be too messy or too slow.

The mechanisms described above account for the large majority of eating problems in young children. In a certain number of cases, however, the feeding difficulty is but one manifestation of a deep-seated emotional problem. An unhappy child, like an unhappy adult, is likely to eat less (sometimes more) than a normal one. Any disturbance in the emotional life of the child may present itself as an eating problem. Excessive demands for attention and spiteful behavior are characteristic of the emotionally disturbed child.

Whereas children with an eating problem generally maintain a normal weight gain, there is often a weight loss where the difficulty is primarily emotional. Such children require careful study. Relief of the eating difficulty will only lead the child to seek outlets for his emotional discomfort in other ways.

Poor appetite sometimes has its origin following an acute infection. In such instances it may require days or even weeks for the appetite to return to normal. At this time the parents are likely to be overly concerned about the child and they need reassurance.

Treatment is successful in the large majority of children. It requires three to four weeks and generally as many visits to educate and reassure the parents.

Treatment depends on a clear understanding of the etiologic mechanisms:

1. The parents should be told about the relatively slow weight gain between one and 5 years of age, the lessened need for food and, consequently, the smaller appetite.

2. There should be no discussion about eating in the child's presence. No attempt should be made to force the child to eat, nor should he be bribed or rewarded. Parents should be urged to forget calories, vitamins, and minerals and rely on the child's appetite. It is reasonable to assume that we were endowed with appetite for some purpose.

3. Children, given a free choice of diet, like meat, butter, fruit, ice-cream, and milk in that order. Their attitude toward vegetables differs just as does adults'. Raw vegetables are often preferred and should be recommended. They

are especially useful for children who are poor chewers. Cereal is the food most often refused and it may be safely omitted from the diet. Excessive ingestion of milk should be avoided. A quart is maximum, a pint adequate. There should be no insistence on this or that food. The food likes and dislikes of children should be respected just as in adults.

Baby food should be avoided. Food should be prepared interestingly. There is no contraindication to fried foods, sauces, and gravies. Young children often prefer highly seasoned and exotic foods like anchovies, olives, etc.

4. The child should feed himself. His table manners will not be good at first but he will learn better by example than by precept.

The food should be served attractively and in small amounts. The child should be permitted to sit at table a reasonable time and the food then removed without comment or show of emotion.

Food, a cracker, fruit, etc., should be given between meals if the child requests it. The punitive attitude implied by "You did not eat your lunch, so now you cannot have anything" should be avoided.

Meals should be served at regular hours. The child should be warned a few minutes ahead of mealtime, so as to avoid taking him away abruptly from interesting play.

Entertainment at mealtime is generally overdone. Certainly excessive antics to entice the child to eat should be discouraged. Nevertheless, eating is, to a large extent, a social function. We all eat better in good company and, when we have to eat alone, we seek some entertainment like reading, listening to the radio, etc. A certain amount of entertainment during mealtime, therefore, is probably desirable for children.

5. Where the feeding difficulty is a manifestation of a deep-seated emotional problem, an investigation of the total situation is necessary. The parents may be overanxious and overprotective because the child has had a previous illness or because there has been a death of a child in the family or because the child is an only one. The parents may be indifferent toward the child or overtly or covertly rejecting. The child may be resentful because of preference for another sibling.

6. Tonics and vitamin supplements to increase appetite should be discouraged. They are not only unnecessary, but they tend to divert parental attention away from the real mechanisms underlying the eating difficulty.

The Social Aspects of Medicine

MEDICAL ORGANIZATION IN NEW ZEALAND

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INTRODUCTION

The author had the good fortune to spend many months in New Zealand during the last war. Observations during two visits and subsequent study of published accounts[1, 2, 3] form the basis of this review of the medical organization and its workings in New Zealand. During the second visit it was possible to spend a week at the Otago Medical School which is located in the town of Dunedin on the east coast of the South Island, and a shorter period at the Capital, Wellington. However, most of the time was spent at Auckland, which is the prosperous town located in the northern peninsula of the North Island. The combination of cordiality and simplicity of the New Zealand people made it possible to become familiar with both the achievements and problems of the medical system. Now that the stresses of war have been ameliorated to a large extent, it is possible to evaluate the effects of this medical system.

With the exception of the Union of Socialist Soviet Republics, Sweden and, to a limited extent, Great Britain, no other country has gone as far as New Zealand in the socialization of medicine. Furthermore, the system is unique and has been in operation for six years. A careful study of what has happened in this important experiment should be extremely valuable to other countries which may embark upon a program of organized medicine. It is more important to bring out the virtues and the faults of the system than to try to balance them in an attempt to pass a verdict.

HISTORICAL

New Zealand is a British dominion with an area of over 100,000 square miles divided between two large and numerous small islands. Closer to Australia than any other continent, it is separated from that country by over a thousand miles of ocean. The climate is, on the whole, temperate, although snow persists throughout the year on the mountain ranges. There is a population of over 1,600,000, of which approximately 6 per cent represents the native Maori peoples. The chief occupations are either pastoral or agricultural.

In 1935, the Labor Party came into power in New Zealand. After two years of negotiation with the New Zealand Branch of the Britain Medical Association, the parliamentary committee investigating health insurance hinted that it was disappointed with the views of the medical association and that it was considering a universal free medical service. Eventually the negotiations broke down and the Social Security Act of 1938 was passed, making provision for the inauguration of medical, hospital, and related benefits. The Social Security Tax of 5 per cent on wages came into effect in 1939 and has been collected ever since then. In fact, the tax has been increased to 7½ per cent.

It is worth mentioning at this time that social security was one of the main issues of the general election of 1939 when the Labor Party won by a large majority. Since that time the Labor Party has been losing votes but social security has not been a political issue.

MENTAL HOSPITALS

The first medical benefit under the Social Security Act, the free hospital treatment of mental patients, came into effect in 1938. Free maintenance and treatment was provided for all patients in public mental hospitals. This meant that fees formerly charged to patients in mental hospitals were paid by the Social Security Fund. Since patient's fees had only accounted for one-fourth of the total revenue of the mental hospitals, there was little change in the cost of treatment or the number of inmates.

MATERNITY BENEFITS

In 1939 the popular maternity benefits came into effect. These include antenatal and postnatal advice or treatment by medical practitioners, and the services of doctors and nurses at confinements. The physician fills in a form with respect to each case of childbirth or miscarriage that he attends, forwards this to the local medical health office, and receives a sum of approximately twenty-five dollars from the Social Security Fund. Extra fees are allowed for complications, accidents, consultations, anesthesia and travel. Obstetrical specialists recognized by the Minister of Health, according to academic qualification and mode of practice, are entitled to collect extra fees from the patient.

In addition to the benefits for medical services by physicians and nurses no charge is made for confinement in any of the public maternity wards. Furthermore, licensed private maternity hospitals are entitled to receive fees from the Social Security Board at the same rates as public hospitals, but may also charge the patient an additional fee.

HOSPITAL BENEFITS

The Hospital Benefit, introduced in 1939, made the services of the public hospitals free to all members of the community. There is no charge to the patient for accommodation, maintenance, medical services, x-ray, diagnostic measures, or treatment. This change was accomplished by payment to the local statutatory Hospital Board of an amount slightly less than two dollars per day for each occupied bed by the Social Security Fund. It should be pointed out that formerly the patient's fees formed only 20 per cent of the hospital revenue, the balance coming from both the local and national governments.

With the inception of Hospital Benefits, the honorary system of hospital staffing was discontinued and the part-time professional staff was given from 800 to 2,000 dollars annually. The full-time staff was not affected by this change.

PHARMACEUTICAL BENEFITS

The Pharmaceutical Benefit was inaugurated in 1941. Any druggist may contract to give this service. The patient merely hands his prescription to the druggist and countersigns it when he receives his medication. The druggist must cost the prescription item by item and send copies to the Government from whom he receives the fee formerly charged to the patient. Insulin, sulfa-drugs and almost all recognized medicaments are on the free list, although the patient must pay the additional cost of proprietary medicines. Prescriptions are limited to one month's supply but may be renewed at the physician's request.

RADIOLOGICAL SERVICES

Both diagnostic and therapeutic x-rays were made free in the public hospitals in 1941. Private radiologists are now entitled to charge the patient a fee equal to the amount which they are allowed to collect from the Social Security Fund as well as collecting this amount from the Fund. A similar practice has been inaugurated for other laboratory services. Physiotherappy is also furnished without cost in the public hospitals.

MEDICAL BENEFITS

This extraordinary portion of the Social Security Act came into effect in 1941, the opposition of the physicians having been overcome by increasing the fee from five shillings to seven shillings and sixpence about $1.35. Service is rendered to the patient on the usual private practice basis and the physician is paid by the Governnment, or the patient pays the physician and receives a refund from the Government. If a higher fee is charged by the physician, the excess must be paid by the patient. Specialists are allowed the same rebate as general practitioners. Extra fees are paid by the Government for travel and calls made at night or on holidays.

DENTAL BENEFITS

It is interesting to note that this system of benefits, which was inaugurated early in 1947, had the approval of the New Zealand Dental Association. These benefits apply chiefly to children of the age 10 to 16 since school dental clinics take care of children up to the age of 10. It is planned to use full-time salaried dentists in these clinics.

FINANCIAL ASPECTS

The cost of the various benefits during the year 1945 to 1946 is shown in Table I. The total cost of social security in New Zealand is about 110 million dollars or approximately seventy dollars per person. This amounts to 10 per cent of individual wages and income. It should be noted that only one third of the social security budget goes to medical health and associated projects.

TABLE I

CATEGORY OF SOCIAL SECURITY	COST IN POUNDS FOR 1945-6	
Maternity benefits	600,209	
Medical benefits	1,427,309	
Hospital benefits	2,173,460	
Pharmaceutical benefits	1,133,366	
Laboratory services	229,971	
Health department	3,031,549	
Mental hospitals	940,166	
Local hospital subsidies	1,251,183	
Total cost of medicine and health	10,787,213	10,787,213
Pensions of aged	9,817,615	
Pensions for widows	1,043,593	
Pensions for invalids	1,193,537	
Pensions for families	2,611,759	
Other civil pensions	1,420,106	
War pensions	3,938,192	
Total cost of nonmedical social security	20,639,634	20,639,634
Total cost of social security		31,426,847

ATTITUDE OF THE PEOPLE

The fact that the social security system has ceased to be a matter of political issue gives an indication that as far as the general public is concerned the system has been well received. This does not mean that there has been no criticism, in fact there has been plenty, among the people as well as the physicians. The shortage of doctors was aggravated by the increased number of people who were made financially capable of getting medical care. The waiting lines were lengthened and the time that physicians could afford to spend with each patient was reduced. Both the patient and the physician were faced with the additional burden of filling out forms for the Government.

EFFECT OF MATERNITY BENEFITS

Maternity benefits are very popular among the people and have enabled women to have larger families, which is important in New Zealand, an underpopulated country. There has been little complaint among the physicians about the single fee for delivery. The system has encouraged patients to have antenatal and postnatal care, a factor which has been appreciated by all concerned.

EFFECT OF HOSPITAL BENEFITS

The hospital benefits have caused considerable criticism from two different aspects.

Crowded conditions in the public hospitals were aggravated by wartime delays in construction work and out-patient work was neglected due to lack of facilities and plans.

Although increased financial assistance was given to the hospitals by the national Government, the local political administration by the statutory hospital boards was not changed. In some instances the Hospital Boards were antagonistic to the physicians and in other cases their administrative work was inefficient.

EFFECT OF THE PHARMACEUTICAL BENEFITS

This benefit was well received by the public and the increase in business made it profitable to the druggists. Such a system with its emphasis on pharmacopeal drugs would have more serious consequences in the United States where proprietary medicines enjoy a wider usage. In 1945-6 the pharmaceutical benefits cost the Government 1,133,000 pounds compared with physician's fees of 1,633,000 pounds paid by the Government. At first this expenditure on medicines seems disproportionately large but in the United States the general public spends as much money on medicines as on physicians' fees.[4]

EFFECT OF RADIOLOGIC AND OTHER BENEFITS

The benefits for radiologic service and other laboratory procedures have not aroused much criticism, although the individual rates established by the Government have come under fire. For example, it is obvious that different x-ray specialists devote different amounts of time and film on the same type of examination, yet each must charge the same fee.

EFFECT OF MEDICAL BENEFITS

This particular benefit has caused extensive and bitter criticism on the part of the physicians who were opposed to it before it was put into practice. A few doctors feel that it is advantageous because it enables patients to make follow-up visits which they would otherwise be unable to afford. However, a majority of the medical men and an even greater proportion of the surgeons dislike the system. This is largely because it encourages persons with slight or imaginary complaints to consult the physician, which has worked a special hardship on all because of the scarcity of available doctors.

THE QUALITY OF MEDICAL CARE

It has been generally conceded that since the medical benefits went into effect, the available medical care has been more equitably distributed, but that the general level of medical care has declined. In most instances the income of doctors has risen, especially that of the general practitioner. It is refreshing to hear the complaint that there is a tendency for general practice to take precedence over specialization, since in the United States the reverse trend is so marked.

MEDICAL EDUCATION

The outstanding criticism which can be leveled against the medical program of the Social Security System is that the latter has come into effect without any provision for increasing the quality or quantity of medical education. This situation is aggravated by the fact that the medical school, although it is excellent, is located far from the centers of population. Until a medical school is opened in Auckland or Wellington, there is little prospect of improving the level of medical care.

THE COST OF MEDICAL CARE

Last but not least, it must be pointed out that the social security system is expensive and that each year it becomes more costly. This factor will, no doubt, form the basis for criticism at home and abroad. However, until the nonmedical portions of the system are made more economical, it is difficult to see much benefit in reducing the medical portion which amounts to about one third of the total cost of social security. Estimates of the cost of medical care in the United States[4] show that about 4 per cent of the national income and thirty-five dollars per capita is spent, compared with 3½ per cent of the income and twenty-three dollars per capita in New Zealand.

NEW DEVELOPMENTS

The medical system in New Zealand was based on a single fee for professional service with a rebate paid by the Government. This plan has been criticized because it does nothing to improve the standard or efficiency of medical service. It is interesting to note that salaried service is now replacing the single fee for service in the new Dental Benefit and in certain local medical services. Apparently there is no evidence of a return to the time-honored system of private practice.

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Editor's Comment

Dr. Roger Lewis had the opportunity to study at first hand the New Zealand experiment in medical care while he was a member of the 18th General Hospital Unit during the recent war. It is appropriate therefore, that he should be the one to report on it in this column.

The New Zealand plan ought to be viewed as an experiment with the fee-for-service system of payment as the basic principle in the system of remuneration of the physician. How does this work in practice and can it ever be made to work in this country successfully? The question is most important to us, because physicians in this country in general are unwilling to think in any other terms. I, therefore, add a little to what Dr. Lewis has written, even though involving repetition, quoting from the recent report by Dr. Douglas Robb, reference to which is given by Dr. Lewis.

The New Zealand plan in brief is that the government provides medical care for everyone by paying for medical and pharmaceutic benefits according to fixed rates. The fee-for-service or "direct claim" system was intended by the government to be standard and has been the one chiefly used, though capitation and salary reimbursement have been employed to some extent. Under the fee-for-service system, the patient signs a form stating that service has been rendered and the physician sends in the form to the health department and

receives 7s, 6 d per service. This is the ordinary arrangement, but many physicians have used a so-called "Refund System" or "Token System," which makes the patient add 3s from his own pocket, so that the physician nets 10s 6 d per service. I shall not discuss the arrangements for specialist or laboratory services, but with this brief explanation will quote from Dr. Robb: "Under these schemes the doctors have become extraordinarily prosperous. It is comparatively easy to work up a good income almost anywhere except perhaps in rural districts where a lot of travelling is still necessary. Actual figures of doctors' incomes are not published, but some which are almost fantastic are commonly mentioned in parliament. The highest rewards are obtainable under a company arrangement, where the principal can pay handsome salaries to juniors and still reap rich rewards. The individual man can make a big income by dint of hard work and organization. . . . From the doctors' point of view perhaps it is a good thing that by ordinary work he can secure very adequate rewards . . . . The emphasis is placed on the number of acts done rather than on quality. Indeed we find the doctor personally doing a number of trifling things in his practice that ought to be done by a nurse or secretary, but are not so done because it is worth 7s 6 d to the doctor, if he does them . . . . The poor man's cough is now as profitable as the rich man's, and certain areas both urban and rural formerly poorly served have now medical men on the spot. So far so good but a further effect is to concentrate medical men in the cities as against country districts where travelling is greater . . . . Moreover, as between general practice and specialists, scientific and teaching work, there is a disproportionate attraction to the former. The pathologists, radiologists, hygienists and teachers in the profession are almost all maintained by salary and are the Cinderellas in the financial sense . . . . The quality of service suffers under the fee-per-service structure with its emphasis on quantity rather than quality. The tendency is toward quick superficial work and the avoidance of difficult subjects, times and places, etc."

The New Zealand experiment teaches lessons: First, the medical care program was thrust on the country by the Labor Government without adequate consultation with medical groups. A chief reason for this was that organized medicine there was not conciliatory to change in medical care, like the British Medical Association in the Lloyd George regime and organized medicine in this country now. Thus, the medical care program was poorly thought out and designed. Second, it was commenced before the organization for medical care the country over was able to cope with it; i.e., it sought solution merely by removal of economic barriers. The rank and file of general practitioners profitted, as is bound to be the case in any medical care system in which the medically indigent become medically solvent and as they will do in this country as soon as the medically indigent group ceases to exist as such. It is astonishing that general practitioners in this country do not see that their incomes will be increased the moment the medically indigent group becomes a secure source of revenue.

So far, I believe, the fee-for-service method of reimbursement in New Zealand has been a failure because it has lowered the standards of medical care, stimulating quantity and not quality of medical practice. However, whatever its defect in administration, it has made general practitioner service available to all and must have given feelings of security difficult to evaluate to low income groups particularly by removing the specter of pauperizing illness. The total success or failure of a medical care program can be measured in just one way; its results on the happiness and health of the people.

It should be added that in the Scandinavian countries the fee-for-service system of payment has been used extensively and with great success. But it has been rigidly controlled.

E. A. P.

Comments on Current Literature

THE ROLE OF FLIES IN POLIOMYELITIS

THE summer incidence of poliomyelitis has been a consistent feature of the natural history of the disease. As early as 1913 Saunders and his associates[1, 2, 3] suggested the importance of flies in the epidemiology of poliomyelitis with special emphasis on the green fly, *Lucilia caesar*.

Subsequently, nonbiting flies collected during epidemics of poliomyelitis in widely separated parts of the country have been found to harbor the virus of poliomyelitis, regardless of the site of collection, whether rural, suburban, or urban. Paul, Trask, Bishop, Melnick, and Casey[4, 5, 6] demonstrated the presence of poliomyelitis virus in emulsions of flies trapped during epidemic periods in Connecticut and Alabama. These pools included the following: *Lucilia, Phormia regina, Musca domestica, Muscina stabulans, Sarcophaga hemorrhoidalis, Ophira leucostoma, Protocaliphora,* and some questionable specimens of *Stomoxys.*

Sabin and Ward[7] were able to isolate the virus of poliomyelitis from flies collected in urban areas during outbreaks of the disease in Atlanta and Cleveland. These investigators considered that the ease with which the virus could be isolated from flies trapped at urban sites where contamination with fecal material, as in open privies, is at least not immediate, places emphasis on the importance of flies in the epidemiology of poliomyelitis, and that flies might be responsible in some measure for the special summer incidence of the disease.

About the same time Toomey, Takacs, and Tischer[8] isolated the virus of poliomyelitis from flies collected in urban areas in Atlanta and Cleveland and from sites near the mouth of a brook which empties raw sewage into Lake Erie and where human excrement is commonly apparent on the surface of the water. In the last instance, a pool consisting of about 2,000 large blow flies and an occasional house fly had been obtained from traps set near the brook which drains parts of the northeastern section of the city where in that year the epidemic made its first appearance. A suspension of these flies contained sufficient virus to produce unmistakable paralysis in monkeys (*Macaca mulatta*) when administered by intracerebral route. The strain of virus was established by passage in monkeys.

Recently Melnick and Penner[9] have reported the experimental infection of flies with human poliomyelitis virus, with YSK strain, with Lansing murine-adapted strain, and with Theiler's virus. Choice of fly species was influenced by the fact that blow flies (*Phormia regina*) and green bottle flies (*Phaenicia sericata*) appeared in all positive pools which had been collected by them in epidemic areas and tested in the laboratory. When murine-adapted strains or the intestinal TO strain of Theiler's virus were fed to flies (*Phaenicia sericata, Phormia regina,* and *Sarcophaga bullata*), virus could be recovered from their bodies and their excreta within seventy-two hours following feeding and for a period of five days thereafter. Isolation from the abdomen was accomplished with greater regularity than from heads and thoraces. When a biologically inert substance such as carmine was fed, excretion occurred in gradually decreasing quantities for six days, only traces remaining in the excreta on the sixth day. The results with a human poliomyelitis virus (NYC-44 strain) were

markedly different. When *Phormia regina* were fed once on a virus preparation from human stools from poliomyelitis patients, virus could be isolated from the bodies of the flies for a period of two weeks and from their excreta for a period of three weeks. All flies used in the experiments were bred in the laboratory. By an ingenious method of handling the flies, food intake could be controlled and measured and excreta collected from each individual. Isolation of virus was accomplished by inoculation of the Siamese monkey, *Macaca irus valida*, the rhesus monkey, *Macaca mulatta*, or the Philippine cynomolgus monkey, *Macaca cynomolgus*.

Results of this type were not obtained with the murine-adapted strains or with Theiler's TO strain of spontaneous encephalomyelitis of mice which behaved in flies in a manner similar to that of a biologically inert substance such as carmine.

The work of Melnick and Penner is of significance since it represents the first controlled study indicating that the human poliomyelitis virus can persist in the body of flies for a considerable period and that the virus can be detected in their excreta. Such experimental results lend support to the concept that the fly may play a real part in the natural history of poliomyelitis. The question whether the fly is an obligatory host or an accidental host or mechanical carrier of the virus of poliomyelitis, and likewise an explanation of the differential behavior of the various strains of virus in the fly must await further investigation.

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News and Notes

The Markle Foundation, which has made many grants in aid of medical research in the past twelve years, has announced a new program beginning in 1947-48. Instead of grants for research, the foundation will inaugurate a "post-fellowship" program to aid young scholars in medical science in order that they may develop as teachers and investigators. Nominations for fellowships will be made by the approved Medical Schools in the United States and Canada and applications from individuals will not be considered. The foundation will set aside $25,000.00 for each fellowship to be expended in a five-year period, and any additional expense in the way of salary and costs of investigations undertaken must be paid by the medical school administering the grant to the individual selected.

Dr. William A. Reilly, assistant clinical professor of pediatrics at the University of California, has been appointed professor and head of the department of pediatrics at the University of Arkansas School of Medicine at Little Rock, Arkansas. Dr. Reilly's appointment is one of a series recently made in line with the University's policy of establishing full-time professorships in its clinical departments.

Dr. James S. Plant, of Newark, N. J., Director of the Essex Juvenile Clinic, died the early part of September. Dr. Plant was an outstanding leader in the field of Child Guidance and Psychiatry, and made many contributions to this phase of pediatrics. He was a frequent speaker at our pediatric meetings.

RESEARCH FELLOWSHIP

The Surgeon General of the **U. S. Public Health Service** has been given the authority to establish and maintain research fellowships. These fellowships are intended to promote the training and development of investigators in the field of medicine and related sciences. Three of the four types are as follows:

A predoctorate research fellowship at the Master level is available to qualified applicants holding a Master's Degree or its equivalent in graduate training. This fellowship carries a stipend, in addition to tuition fees, of $1,600 for persons without dependents and $2,000 for persons with dependents.

These predoctorate fellowships are also granted to medical students who, having completed one or two years of their medical course and contemplating a career in medical research, wish to spend one, two, or three additional years in a basic science (biochemistry, physiology, physics, etc.) before completing their studies toward the M. D. degree.

A postdoctorate research fellowship is awarded to qualified persons holding a Doctor's Degree in medical or related fields. This fellowship does not provide tuition fees but carries a stipend of $3,000 per year for Doctors without dependents and $3,600 per year for those with dependents. An increase of $300 each year is granted to those Doctorate Fellows who are reappointed.

Special research fellowships are awarded to applicants who qualify for a postdoctorate fellowship and in addition have demonstrated outstanding ability, or who possess specialized training for a specific problem. This fellowship does not carry a set stipend but is determined in the individual case.

Term of Fellowship.—Fellowships are awarded for one-year periods and may be renewed. Except in unusual circumstances, Postdoctorate Fellows are not reappointed for a third year.

Further details may be obtained from Dr. C. J. Van Slyke, Chief, Division of Research Grants and Fellowships, National Institute of Health, Bethesda, Md.

THE HOSPITAL PROGRAM

The Hospital Survey and Construction Act, which became law in August, 1946, has launched the most comprehensive program in the history of this country for the construction of hospitals and health facilities. To help communities realize the benefits of this legislation, the U. S. Public Health Service has just issued a series of five pamphlets.

The Hospital Survey and Construction Act is a summary of the law and regulations. *Why We Need More Hospitals* gives the story of hospital needs in this country. *The Hospital Act and Your Community* tells in simple terms what the program means to states and communities. *Hospital Quiz* is a series of questions and answers on hospital planning. *What Is a Hospital System?* describes a coordinated hospital system, intended to extend the scope of hospital care. Sample copies of these pamphlets are available free on request to the U. S. Public Health Service, Washington 25, D. C.

Book Reviews

1946 Year Book of Pediatrics. Isaac A. Abt and Arthur B. Abt, editors, Chicago, 1947, Year Book Publishers. Price $3.75.

1946 Year Book of Endocrinology, Metabolism, and Nutrition. Willard O. Thompson and Tom D. Spies, editors, Chicago, 1947, Year Book Publishers. Price $3.75.

These two volumes of the Year Book series are the ones of chief interest to pediatricians. The one on pediatrics is similar to past issues and may be of value to those who like their information in concentrated doses. The many articles reviewed are not critically discussed and hence there is a mingling of the important with the unimportant.

To the volume on Endocrinology, which, as in past years, is edited by Dr. Thompson, a section on metabolism and nutrition, edited by Dr. Tom Spies, has been added. The newer advances as those of the use of folic acid are well covered.

Science and Seizures. William G. Lennox, New York, 1946, Harper and Brothers. Price $2.00.

A second edition of Dr. Lennox' book on epilepsy and migraine for the lay reader. In the new edition the advances since the first edition in 1941, as Tridione, are considered. The information is sound and the book can be recommended to the parents of children with epilepsy who are faced with many problems of the present and the future. Of particular interest is the discussion of the complex problem of heredity and marriage, a problem which every physician with an epileptic patient must sooner or later face.

Nutrition and Vitamin Therapy in General Practice. Edward S. Gordon, Chicago, 1947, Year Book Publishers. Price $5.00.

A third edition bringing up to date the developments in our knowledge of vitamins and food which have taken place since the second edition in 1942. There is an excellent chapter on weight control.

Rocky Mountain Conference on Infantile Paralysis. Denver, 1947, University of Colorado School of Medicine, pp. 199. Price $1.25.

A volume containing the papers presented at the conference held in Denver in December, 1946, sponsored by the University of Colorado School of Medicine and the National Foundation for Infantile Paralysis. In addition to the local participants from the medical school, a group of eleven well-known authorities in the field of poliomyelitis from other parts of the country took part, and the report carries fourteen of the papers presented, together with the discussion. Practically every phase of poliomyelitis was covered, including the epidemiology, pathology, diagnosis, and treatment. The volume is of interest to all working in the field of poliomyelitis and may be obtained from the University of Colorado Medical School.

Editor's Column

Two new departments will be found in this issue of the JOURNAL. Dr. Harry Bakwin, of the department of pediatrics at New York University, will edit a department devoted to discussion of the psychologic and behavior problems of infancy and childhood which form such an important part of the work of the physician who cares for children.

Dr. Russell J. Blattner, head of the department of pediatrics at Baylor University, Houston, Texas, will comment each month on some topic of interest and importance in current medical literature.

The two departments, one on Medical Care, or, as has been suggested as a title, Medical Management, and the other, Clinical Conferences which were tried out in the July number of the JOURNAL, have met with the approval of many subscribers, as indicated by their replies to the editorial in that issue. Accordingly, plans are being made to continue them at fairly regular intervals, and a number of clinics and individual pediatricians are now preparing material for publication.

INFLUENZA VACCINATION

As the winter season approaches, the question of vaccination against influenza will be brought up by many parents whose interest has been aroused this past year through articles in the lay press. The report of a study committee on influenza vaccination of the A.P.H.A.,* headed by Dr. Thomas Francis, Jr., which was published in the September issue of the *American Journal of Public Health,* may be of service to the practitioner in answering some of the questions which will be asked.

Studies at Ann Arbor in 1945 showed that the incidence of influenza infection in a group of 600 students vaccinated against influenza A and influenza B was 1.1 per cent, and in a control group of 1,100 was 9.9 per cent. At Yale, groups of a similar size had an incidence of 0.5 per cent for the vaccinated and 12.5 per cent for the unvaccinated.

Resistance in the vaccinated is not limited to four or six weeks after vaccination, but may exist for a longer period in some individuals. The mean antibody response reaches its height about two weeks after the vaccination and declines to about one-third of the peak level in four to five months.

The vaccine is seemingly of a specific nature against influenza A and influenza B, but there is no evidence that it influences the common cold or other unidentified respiratory infections.

There is a local reaction to the vaccine but less than one per cent develop a febrile condition. Children are more prone to febrile reactions than adults. The vaccine is prepared from the allantoic fluid of the developing chick which is not highly sensitizing. Yolk or egg white may accidentally enter in the

*Am. J. Public Health 37: 1013, 1947.

course of the production, and anaphylactic reactions have occurred in individuals with asthma or urticarial sensitivity to chicken and eggs. Careful history of such sensitivity should be obtained before giving the vaccine, but the suggestion that all individuals receive skin tests before vaccination seems unnecessary in the opinion of the committee, if other precautions are observed, as having epinephrine and other antispasmodics readily available. Data at present do not suggest a prominent sensitizing effect of the vaccine on persons revaccinated one or more times.

The suggested dose for children under 5 years of age is 0.1 to 3 ml.; from 5 to 10 years 0.5 ml.; and above 10 years the adult dose of 1.0 ml.

Influenza A has occurred in epidemic form at intervals or two to three years and influenza B at intervals of four to five years, but the time of recurrence can not be rigidly predicted. The resistance produced by vaccination is not known to persist effectively from one season to another. For these reasons, and taking the expense into consideration, the general employment of the vaccine is not warranted administratively by health departments at the present time. On the other hand, the committee feels it is desirable for certain groups, such as older individuals in whom the fatality rate is high, essential public service personnel, and institutional and university groups where the facilities for the care of the sick are limited. The highest incidence of the disease is in children, but the mortality rate is extremely low.

The question of when the vaccine should be given is open to discussion. Full advantage for a large population only seems possible by vaccination in advance. In institutions or closely knit groups it might be withheld until evidence is obtained that epidemic influenza is occurring. Against this is the speed at which the epidemic spreads, and the interval of at least a week between vaccination and its effect.

In connection with this report of the study committee, another communication by Francis and his associates* from the University of Michigan, reporting on their experience with influenza vaccination in the spring of 1947, is important. In the fall of 1946, 10,328 students were vaccinated against influenza A and B, and 7,615 unvaccinated served as a control. Early in March, 1947, an epidemic of respiratory disease developed. Between March 3 and April 4 the case incidence was 7.19 per cent vaccinated and 8.09 per cent for the unvaccinated. From serologic studies it was evident that the infection was due to the influenza virus. The ineffectiveness of the vaccine in preventing influenza in the 1947 epidemic was not apparently due to the time interval between its administration and the onset of the epidemic, but rather to the lack of sufficient antigenic crossing between the strains of virus in the vaccine and the prevalent strain responsible for the epidemic.

One can only conclude that as yet influenza vaccination is in its experimental stage, and its widespread uncontrolled use as a routine measure does not seem justified.

*Am. J. Public Health 37: 1109, 1947.